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Case reports in nephrology

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Case reports in nephrology

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Editorial: Case reports in nephrology

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Editorial on the Research Topic
Case reports in nephrology

Case reports are an important source of information and learning in the medical literature. These are also usually the first publications by many doctors in their academic careers. Though, in the era of evidence-based medicine, case reports are lower down in the hierarchy of evidence, they form a unique way of sharing experiences and anecdotal associations that can then be subjected to more rigorous analysis. In this issue, we have compiled unique and interesting case reports related to the field of nephrology that will be relevant in clinical practice and will be of interest to nephrologists and physicians alike.

Pregnancy and renal diseases

There has been a steady increase in the success rate of pregnancy among patients on dialysis since the 1980s (1). Improvements in dialysis technology and adequacy along with better drug therapy and nutritional management have made this possible. Pregnancy just before the initiation of dialysis and in the 1st year of it is likely to be successful.

In an interesting case report, Mambap et al. reported a successful pregnancy while on dialysis for 11 years. The pregnancy was maintained until 36 weeks, when a healthy 2,270 g female baby was delivered by elective cesarean section for tight nuchal cords and intrauterine growth retardation. The mother maintained well in the last follow-up of 4 years, and the child was healthy.

In another case report by Kondakova et al., breast milk was evaluated before and after dialysis in a 31-year-old woman who had a successful delivery while on dialysis. The authors did not reveal an optimal time interval for breastfeeding a baby. Furthermore, they opined that breastfeeding is not advisable since the concentration of nutrients is low, and the content of toxic substances exceeds the permissible limits.

One of the major renal emergencies during pregnancy is renal colic due to calculous renal disease. Cystinuria is a rare genetic disorder that is characterized by excessive urinary excretion of cystine. It predominantly affects men compared to women. Ivandic et al. described a case of a 38-year-old woman with cystinuria who manifested cystine stones during her third pregnancy, with a very complicated course and several urological interventions during pregnancy due to the formation of new stones and worsening of kidney function. Despite all the complications during the pregnancy, she successfully delivered a healthy girl.

Genetic diseases and the kidney

Autosomal dominant tubulointerstitial kidney disease due to UMOD mutations (ADTKD-UMOD) is a rare condition associated with end-stage kidney disease (ESKD). It is majorly seen among adult men. Li et al. reported a 13-year-old young girl with unexplained chronic kidney disease and no positive family history. Trio whole-exome sequencing confirmed that she carried a *de novo* heterozygous mutation c.280T>C (p.Cys94Arg) in the UMOD gene. Due to a lack of targeted therapy, she was treated with conservative therapy of chronic kidney disease (CKD). This case illustrates the value of whole-exome sequencing in a patient in whom the cause of CKD is not clear, especially during childhood.

Infection and the kidney

The most common bacterial infection following renal transplantation is urinary tract infection (UTI), including pyelonephritis, ranging from 7 to 86% of all renal transplant recipients (2). It is associated with excess risk of graft loss and death. Emphysematous pyelonephritis (EPN) is a severe, acute necrotizing infection that is defined by the presence of gas in the kidney parenchyma. Multiple case reports have described both the radiologic features and clinical course of native kidney EPN. Abu Jawdeh et al. reported a case of EPN in a renal transplant recipient. It was further complicated by multiorgan failure and finally required graft nephrectomy. This case highlights the poor outcome of EPN in the post-renal transplant setting. Transplant kidneys, being the solitary functioning kidney, may not respond well to antibiotic therapy when they develop EPN and may require graft nephrectomy, resulting in loss of the functioning graft. This case emphasizes the need for definite strategies aimed at reducing UTI and pyelonephritis in renal transplant recipients, which will further improve transplant outcomes in the long run.

AKI

Globally, 13 million people worldwide are thought to be affected by acute kidney injury (AKI) every year. It is well established that AKI is associated with adverse outcomes, including development or worsening of CKD, cardiovascular events, and mortality. Several complications have been reported in association with AKI. Community-acquired AKI has a varied etiology and milder course compared to hospital-acquired AKI (3). Indigenous substances are one of the frequent causes of AKI, especially in the developing world, where there is high dependence on alternative medicines and faith healers. Torabi Jahromi et al. reported a rare case of a 35-year-old woman presenting with renal arcuate vein thrombosis (RAVT) and acute kidney injury (AKI) following upper respiratory tract symptoms and toxic substance ingestion. Renal biopsy suggested venous thrombosis in the renal arcuate veins. The patient's symptoms resolved following anticoagulation with apixaban, a direct oral anticoagulant. Though there are a limited number of studies showing the concurrent presentation of RAVT and overt AKI in patients following ingestion of nephrotoxic agents, this case illustrates the necessity of the early evaluation of etiology and appropriate management to prevent progression to CKD.

Wang L. et al. reported AKI following a medicinal herb leading to acute oxalate nephropathy (AON). This case highlights the need for a thorough medication history, including the history of use of medicinal herbs in all patients with community-acquired AKI. The use of medicinal herbs with unknown oxalate contents increases the risk of AON and should be avoided.

Complications associated with CKD

Tripterygium wilfordii is a traditional Chinese herbal medicine that is used to treat several diseases, including CKD, rheumatic autoimmune disorder, and skin disorders. Zhang et al. reported the first case of a 50-year-old Chinese female with ESRD who developed severe bone marrow suppression after taking a short-term normal dose of a T. wilfordii-containing decoction. She died of sepsis and septic shock, although timely therapeutic measures (e.g., stimulating hematopoiesis, anti-infection treatment, and hemodialysis) were administered. This case contradicts the notion that side effects of Chinese herbs on the hematopoietic system are non-lethal and points out that patients with ESRD are at higher risk of such complications.

CKD leads to defects in divalent ion metabolism, leading to secondary hyperparathyroidism characterized by hypocalcemia and hyperphosphatemia. Sevelamer carbonate is the most widely used non-calcium-based phosphate binder. Gastrointestinal (GI) injury associated with sevelamer use is a documented adverse effect but is underrecognized as a cause of life-threatening GI complications. Fistrek Prlic et al. reported the case of a 74-year-old woman taking low-dose sevelamer with serious GI adverse effects causing colon rupture and severe GI bleeding. This case documents an important adverse effect of a frequently used drug in nephrology practice and cautions against its use in elderly people with risk factors for GI complications.

Nephrotic syndrome

Minimal change disease (MCD) is one of the common causes of idiopathic nephrotic syndrome (INS), accounting for 10–20% of INS in adults. Rituximab has been used successfully in patients with autoimmune hemolytic anemia (4). Zhuang et al. reported the case of an adult patient with refractory MCD complicated with β-thalassemia minor and accompanied by autoimmune hemolytic anemia. The patient had a frequently relapsing course with steroids and ultimately achieved clinical complete remission after the administration of rituximab. Moreover, anemia due to mild β-thalassemia also recovered to normal. The disease situation remained stable during the 36 months of follow-up. These findings suggest that rituximab may contribute to the improvement of steroid-dependent or frequently relapsing MCD and anemia in β-thalassemia minor accompanied by autoimmune hemolytic anemia.

Idiopathic multicentric Castleman disease (iMCD) is a systemic and polyclonal lymphoproliferative disease, leading to the overproduction of interleukin-6 (IL-6), that involves multiple

organs, including the kidneys. Previous reports suggested that excessive IL-6 actions in iMCD have a causal relationship with the development of diverse histopathological renal manifestations, which cause nephrotic syndrome. Kojima et al. reported a series of three cases of nephrotic syndrome due to iMCD that help to delineate the importance of early and continuous therapy with the anti-interleukin-6 receptor antibody tocilizumab. All three patients presented with nephrotic syndrome, and renal biopsy showed diffuse mesangial and endocapillary hypercellularity without immune deposits, along with AKI in one and immune-complex glomerulonephritis with AKI in another. The third case was diagnosed with nephrotic syndrome secondary to membranous glomerulonephritis, with IgE antibodies to tocilizumab, and was therefore treated with prednisolone alone. In contrast to the first two cases, the third progressed to ESRD. This case series suggests the necessity of maintaining clinical vigilance for iMCD as a possible underlying component of nephrotic syndrome and the prompt initiation and continuous administration of tocilizumab.

Nephrotic syndrome with dual etiology in a single patient is not a usual entity. Wang Y. et al. described a 39-year-old male patient with IMN combined with immunoglobulin light-chain amyloidosis nephropathy who presented with nephrotic syndrome. Renal pathology revealed MN. A positive Congo red staining and the pathognomonic apple-green birefringence under cross-polarized light were considered to be associated with amyloid nephropathy. Immunofluorescence showed that the λ light chain was positive. His serum was negative for antibodies against the Phospholipase A2 receptor (PLA2R), but PLA2R was present in the renal tissue. It is very interesting to note the dual pathology and management becomes crucial in such situations.

Association between nephrotic syndrome and malignancies is not unusual, but more cases have been reported with membranous nephropathy. Cai et al. reported a patient with MCD simultaneously associated with papillary thyroid carcinoma (PTC). After surgery, MCD remitted rapidly and completely, strongly suggesting the diagnosis of MCD secondary to PTC. This case highlights the importance of tumor screening wherever indicated and avoiding conventional therapy with steroids in cases of MCD.

COVID vaccine and the kidney

There are numerous reports of renal diseases occurring after COVID vaccination (5). Zamoner et al. reported a case of anti-neutrophilic cytoplasmic antibody (ANCA)-positive crescentic glomerulonephritis 5 days following vaccination with the Oxford–AstraZeneca COVID-19 vaccine in a 58-year-old female patient. She was treated with steroids and cyclophosphamide, leading to the stabilization of the creatinine. Early detection and prompt institution of therapy are key to restoring complications following COVID-19 vaccination.

Author contributions

SR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MR: Supervision, Writing – original draft. SM: Conceptualization, Supervision, Writing – original draft.

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ANCA-associated vasculitis following Oxford-AstraZeneca COVID-19 vaccine in Brazil: Is there a causal relationship? A case report

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This article presents a case of rapidly progressive glomerulonephritis following the Oxford-AstraZeneca COVID-19 vaccine in a female patient 58 years old. After 5 days, she presented fatigue, paleness, arthralgia on hands, knees, ankles, foamy urine, and elevated blood pressure. Exams showed serum creatinine of 2.2 mg/dL (baseline creatinine of 1.0 mg/dL). Urinalysis revealed hematuria, and her 24-h urinary protein excretion was 4.4 g. Additional exams showed hypercholesterolemia, severe anemia, and normal serum albumin. Testing of antineutrophil cytoplasmic antibodies anti-myeloperoxidase was positive at a titer of 1/80. Serum and urine protein electrophoresis and other exams showed no alterations. She was started on steroid pulse therapy after worsening kidney function, reaching serum creatinine of 3.3 mg/dL. A kidney biopsy revealed crescentic glomerulonephritis with glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy. Induction therapy was given with intravenous cyclophosphamide 0.5 g/m^2 for 6-monthly pulses, followed by maintenance therapy with oral azathioprine at 2 mg/kg and prednisone tapering. The patient did not develop any complications during the induction therapy, and is currently on maintenance therapy with a serum creatinine of 1.87 mg/dL.

KEYWORDS

acute kidney injury, COVID-19, vaccine, Oxford, AstraZeneca

Introduction

Coronavirus (SARS-CoV-2) infection, named COVID-19, was detected for the first time in China in December 2019 and has affected over 380 million people worldwide, causing over 5.7 million deaths. In Brazil, over 25.7 million cases and 628 thousand deaths have been reported, primarily from Severe Acute Respiratory Syndrome.

The pandemic caused a significant social impact, and the search for immunization became fundamental.

Although acute kidney injury related to COVID-19 infection is frequent, its association with vaccines is rare. This article presents a case of rapidly progressive glomerulonephritis following vaccination.

Case report

The patient was female, 58 years old, with a previous medical history of hyperthyroidism treated in 2006, and at the moment of evaluation, not on any medication. She received the first dose of Oxford-AstraZeneca Covid vaccine and developed a minor reaction (myalgia and pain on the injection site) in the following 2 days. After 5 days, she presented fatigue, paleness, arthralgia on hands, knees, ankles, foamy urine, and elevated blood pressure.

Due to persisting systemic symptoms, she sought medical attention. Investigation revealed a serum creatinine of 2.2 mg/dL, urea of 67 mg/dL, a significant elevation compared to a baseline creatinine of 1.0 mg/dL. Urinalysis revealed hematuria (20 to 25 red blood cells per high power field) and proteinuria (2+). The 24-h urinary protein excretion was 4.4 g. Additional investigations showed hypercholesterolemia, severe anemia, and normal serum albumin. There was a hematological investigation, with negative hemolysis tests, marrow aspirate and immunohistochemistry demonstrating reactive marrow, absence of myelodysplasia or neoplasia in the sample. Because of the evidence of altered kidney function, she was referred to a Nephrologist.

Ultrasound showed kidneys with 10.5 cm long and parenchyma 1.6 cm size. Antinuclear antibody test (ANA) and anti-double-stranded DNA (anti-dsDNA) were negative. The serum complement (C3 and C4) were within normal limits, and testing of antineutrophil cytoplasmic antibodies (ANCA) anti-proteinase 3, anti-glomerular basement membrane (GBM) and viral serologies were negative. However, anti-myeloperoxidase was positive at a titer of 1/80. Serum and urine protein electrophoresis showed no alterations.

She was started on steroid pulse therapy after worsening kidney function, reaching serum creatinine of 3.3 mg/dL and indicating possible rapidly progressive glomerulonephritis (RPGN). She received 1 gram of methylprednisolone daily for three consecutive days in an outpatient setting, followed by 1 mg/kg of oral prednisone. She required a blood transfusion, vitamin B12, folic acid supplementation, and medication to reduce blood pressure during follow-up.

A kidney biopsy was performed 15 days after initiation of treatment and 80 days after vaccine administration (Figure 1) and revealed crescentic glomerulonephritis with glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy (Figures 1A,B). We also observed in the glomeruli active inflammatory lesions characterized by endothelial swelling, endocapillary proliferation, accumulation of macrophages, hyaline deposits and cellular e fibrocellular crescents (Figures 1B–D). Immunofluorescence confirmed nonspecific entrapment with C3 positive in sclerotic areas.

After the biopsy, induction therapy wasgiven with intravenous cyclophosphamide 0.5 g/m^2 for six-monthly pulses

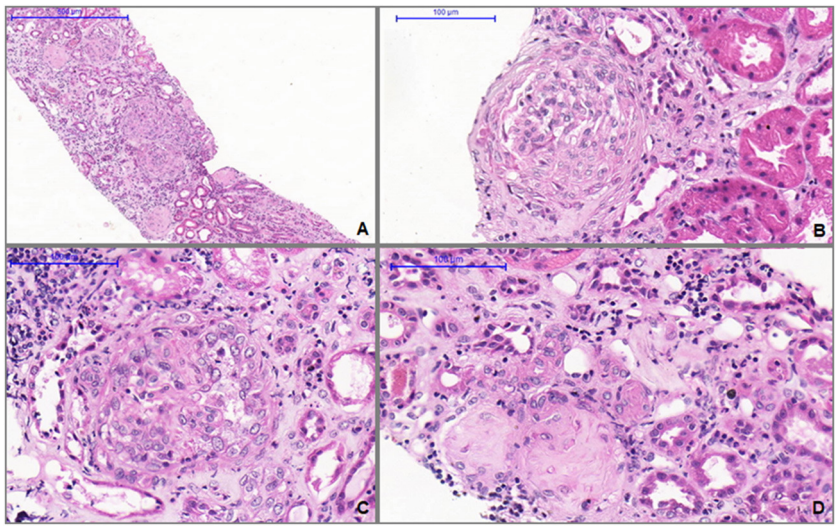

FIGURE 1
(A) Light microscopy shows glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy (H&E, 100X). **(B)** Glomerulus with fibrocellular crescents (H&E, 400X). **(C)** Active glomerular lesion showing endo and extracapillary hypercellularity (H&E, 400X). **(D)** Thickened and tortuous arteriole associated with globally sclerotic glomerulus and extensive parenchymal atrophy and fibrosis (H&E, 400X).

followed by maintenance therapy with oral azathioprine at 2 mg/kg and prednisone tapering.

The patient did not present any complications during the induction therapy, and outpatient follow-up continues maintenance therapy with a current serum creatinine of 1.87 mg/dL.and with 24-h urinary protein excretion of 0.5 g.

Discussion

As vaccination advances, some side effects have been reported (1–3). Most common among them are tenderness on the injection site, fever, fatigue, myalgia, and headaches (2). The association between COVID-19 and kidney impairment has been well established.

Some vaccines have been associated with the development of autoimmune diseases following immunization, including reports of ANCA-associated vasculitis (AAV) after Influenza vaccination (1, 3). AAV is characterized by small-vessel vasculitis and the presence of antineutrophil cytoplasmic antibodies (2). To this date, episodes of AAV following the vaccines from Pfizer (1) and Moderna (4) have been reported.

The mechanism behind this association is uncertain. It could be explained by molecular mimicry, polyclonal activation of B cells, or transient proinflammatory cytokines response, leading to autoimmune diseases in genetically predisposed individuals (2, 5).

The biopsy identified changes in appearance in chronification, compatible with the degree of aggressiveness of lesions of increasing vasculitis with significant impairment of renal function. The unclear etiology of anemia was also identified with the possible contribution of systemic inflammatory reaction.

Here we presented a case of AAV following immunization against SARS-CoV-2 with the Oxford-AstraZeneca vaccine. Although this was a temporally related fact in a patient with previously normal renal function, suggesting de novo vasculitis, it is impossible to rule out previous renal alterations due to vasculitis or other undiagnosed issues. Causality is based solely on temporal precedence, as a direct correlation to the vaccine cannot be proved.

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 studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa - Faculdade de Medicina de Botucatu. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WZ, JS, and BD contributed to conception and design of the study. AM and VS organized the database. WZ, JS, BD, and AM wrote the first draft of the manuscript. AG, DS, and RV wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Idiopathic membranous nephropathy with renal amyloidosis: A case report

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Background: Immunoglobulin light chain amyloidosis is a clonal, non-proliferative plasma cell disorder, in which fragments of immunoglobulin light chain are deposited in tissues. Clinical features depend on organs involved but can include restrictive cardiomyopathy, nephrotic syndrome, hepatic failure, peripheral/autonomic neuropathy, and atypical multiple myeloma. Membranous nephropathy (MN) is a group of diseases characterized by deposition of immune complexes under the epithelial cells of glomerular basement and diffuse thickening of the basement membrane. Most patients with idiopathic MN (IMN) have been exposed to phospholipase A2 receptor (PLA2R) antigen, and anti-PLA2R antibodies that attack podocytes can be detected in their blood. IMN combined with amyloidosis nephropathy without secondary factors is rare. The present study describes a patient with IMN combined with immunoglobulin light chain amyloidosis nephropathy.

Case report: A 39-year-old man was admitted to our hospital because of weight loss and edema. His clinical manifestation was nephrotic syndrome. Renal pathology revealed MN. A positive Congo red staining and the pathognomonic apple-green birefringence under cross-polarized light were considered to be associated with amyloid nephropathy. Immunofluorescence showed that λ light chain was positive. Heavy chain deposition disease and amyloid-associated protein amyloidosis were excluded by immunofluorescence and immunohistochemistry, respectively. Subsequent examinations showed that his serum was negative for antibodies against the PLA2R, but PLA2R was present in renal tissue. The final diagnosis was IMN with light chain amyloid nephropathy.

Conclusion: Renal amyloidosis accompanied by IMN is uncommon. Attention should be paid to the subtype of the disease and the exclusion of secondary factors. Perfect clinical and pathological examination are helpful

for the classification and staging of the disease. Congo red staining, light microscopy, immunofluorescence, immunohistochemistry, electron microscopic examination, pathological tissue staining for PLA2R antigen and testing for anti-PLA2R antibody in serum are helpful.

KEYWORDS

idiopathic membranous nephropathy, renal amyloidosis, phospholipase A2 receptor, renal biopsy, case report

Introduction

Amyloidosis are diseases of protein conformation, caused by misfolding and aggregation of autologous proteins that deposit in tissues as amyloid fibrils. Amyloid immunoglobulin light chain (AL) amyloidosis is characterized by a clonal population of bone marrow plasma cells that produce a monoclonal kappa (κ) or lambda (λ) light chain (1), with determination that amyloid is composed of immunoglobulin light chains required for diagnosis (2). More than 75% of patients with systemic amyloidosis patients have AL amyloidosis, with about 65% of the latter showing kidney involvement (3). The primary manifestation of renal amyloidosis is the deposition of amyloid substances in the glomeruli, which may be accompanied by deposition in the renal interstitium and vascular wall.

Membranous nephropathy (MN) is an autoimmune disease caused by the deposition of immune complexes under epithelial cells of glomerular basement. Podocytes in these patients are specifically attacked by antibodies against phospholipase A2 receptor (PLA2R). The pathogeneses of idiopathic MN (IMN) and amyloidosis nephropathy are different (4). The present study describes a patient who presented with nephrotic syndrome (NS), which was subsequently diagnosed as IMN with renal amyloidosis.

Case presentation

A 39-year-old Chinese man was admitted to our nephropathy department with weight loss for the previous 1 year and edema for 40 days in April 2018. His appetite was poor and his consumption of meat was reduced. Edema was observed in both lower extremities. He was diagnosed at a local hospital with hypoproteinemia and proteinuria, and was prescribed cephalosporin and a diuretic, but there was no obvious improvement. He had no history of kidney disease, no history of other systemic or genetic diseases and had no psychosocial history. During the course of the disease, he experienced occasional flustering and bloating. His daily urine volume was about 600 ml. His weight had dropped 10–15 kg during the previous year. Physical examination showed that his blood pressure was 99/68 mmHg, he had a bulging abdomen, and he had severe edema in his lower extremities. Other results of physical examinations were within normal limits.

Laboratory parameters at the time of kidney biopsy are shown in **Table 1**. His serum creatinine was 95.3 μmol/L and serum albumin was 13.1 g/L. The daily urine protein excretion was 8.01 g/24 h, the daily urinary secretion of κ light chain was 90.10 mg/24 h, and λ light chain was 141.10 mg/24 h. The serum free-κ and free-λ chains were 27.10 mg/L and 145.00 mg/L, respectively. An electrocardiogram indicated low and inverted T waves. The chest computed tomography (CT) showed bronchitis, slight inflammation of the lungs, slight enlargement of the mediastinal and right hilar lymph nodes, coronary calcification, and ascites. Urinary color Doppler ultrasound suggested enhanced echogenicity of the renal cortex and ascites, and that the maximum depth in the dark region of the lower abdomen was 100 mm. Color Doppler echocardiography showed that there were no obvious abnormalities in cardiac structure and blood flow. No obvious abnormalities were found in other laboratory indicators (see **Table 1** for details). Hepatitis B virus, hepatitis C virus, human immunodeficiency virus and syphilis antibody were negative.

Renal biopsy was performed on May 2, 2018. Light microscopy showed 38 glomeruli, one was spherical sclerosis, whereas in the remaining glomeruli, there was small amounts of erythrophilin deposition under the epithelial cells (**Figures 1A,B**). The glomeruli had diffused mesangial broadening, and an eosinophilic homogeneous non-structural substance was found to be deposited diffusely in mesangial areas and capillary walls (**Figure 1C**). The basement membrane thickened segmentally, but there were no absence of spike formation and no eyelash structure in the glomerular basement membrane (GBM) (**Figure 1D**). Large numbers of lymphocytes and macrophages were found to have infiltrated in renal interstitium focally, accompanied by slight fibrosis. Small

Abbreviations: MN, Membranous nephropathy; IMN, Idiopathic membranous nephropathy; PLA2R, Phospholipase A2 receptor; AL, Amyloid immunoglobulin light chain; κ, Kappa; λ, Lambda; NS, Nephrotic syndrome; CT, Computed tomography; GBM, Glomerular basement membrane; AA, Amyloid-associated protein.

TABLE 1 Laboratory parameters at the time of kidney biopsy.

Laboratory parameter	Value	Units	Normal range	Finding
Platelets	450	10^9/L	125–350	High
Hemoglobin	171	g/L	130–175	Normal
γ-Glutamyl transpeptidase	226.8	U/L	10.0–60.0	High
Cholinesterase	12,658	U/L	4,300–12,000	High
Total protein	42.1	g/L	65.0–85.0	Low
Serum albumin	13.1	g/L	40.0–55.0	Low
Albumin/Globulin ratio	0.45		1.2–2.4	Low
Blood urea nitrogen	5.36	mmol/L	3.1–8.0	Normal
Creatinine	95.3	μmol/L	57–97	Normal
Blood uric acid	532	μmol/L	208–428	High
Cystatin C	1.31	mg/L	0.38–1.26	High
Cholesterol	19.29	mmol/L	2.6–6.0	High
Triglyceride	4.98	mmol/L	0.28–1.80	High
Low density lipoprotein cholesterol	11.36	mmol/L	2.06–3.10	High
Blood calcium	1.94	mmol/L	2.11–2.52	Low
Urinary proteinuria	3 +		NA	High
Urinary sediments red blood cell	13.1	/HPF	0.0–3.0	High
Urine cast	46	/LPF	0–2	High
Urinary protein excretion	8.01	g/24 h	<0.20	High
Urine microalbumin	6570.50	mg/24 h	0–60	High
Urine α1 microglobulin	70.64	mg/24 h	<24	High
Urine β2 microglobulin	0.4	mg/24 h	<0.4	High
Urine IgG	260.95	mg/24 h	0–17.0	High
Urine free κ light chain	90.10	mg/24 h	<14.20	High
Urine free λ light chain	141.10	mg/24 h	<7.80	High
Thyroid stimulating hormone	20.000	uIU/ml	0.27–4.2	High
Free triiodothyronine	2.96	pmol/L	3.1–6.8	High
Free thyroxine	8.49	pmol/L	12.0–22.0	High
Serum IgG	3.06	g/L	7.0–16.0	Low
Serum IgA	3.47	g/L	0.7–4.0	Normal
Serum IgM	2.50	g/L	0.4–2.3	High
C3	1.80	g/L	0.9–1.8	Normal
C4	0.75	g/L	0.1–0.4	High
Erythrocyte sedimentation rate	47	mm/1 h	0–15	High
Serum protein electrophoresis	Normal		NA	Normal
Urine immunofixation electrophoresis	Normal		NA	Normal
Blood immunofixation electrophoresis	Normal		NA	Normal
Serum free-κ chain	27.10	mg/L	6.7–22.4	High
Serum free-λ chain	145.00	mg/L	8.3–27.00	High
Brain natriuretic polypeptide	264.0	pg/ml	0–125	High
Myoglobin	41.7	ng/ml	0–121	Normal
Creatine kinase-myoglobin	0.88	ng/ml	0–3.38	Normal
Cardiac troponin I	0.020	ng/ml	0–0.034	Normal
Carbohydrate antigen 125	459.86	U/ml	<35.00	High
Neuron specific enolase	34.06	ng/ml	<25.00	High

amounts of eosinophilic homogeneous non-structural deposits were observed in the interstitium and in some arteriole walls, with slight thickening of some arterioles (Figure 1C). Congo red staining showed that the glomeruli, partial arteriole wall and local interstitium were positive (Figure 1E). Pathological apple-green birefringence was produced under cross-polarized light (Figure 1F). Immunohistochemistry showed positive expression fine granular deposition of PLA2R along the capillary walls (Figure 1G). It also showed positivity for λ and slight positivity for κ. Immunohistochemical staining of paraffin sections showed that amyloid-associated protein (AA) was negative in the mesangial area of the glomeruli and arteriolar wall, as well as in the focal renal interstitium (Figures 1H,I is the positive control). Immunofluorescence showed granular deposition along the glomerular capillary wall with very strongly positive for IgG (Figure 2A), strongly positive for IgM, slightly positive for IgA, and negative for C3, C4, C1q, and fibrinogen. The small arteries, glomerular mesangial area, and capillary walls were strongly positive for λ (Figure 2B), with κ deposits observed along the glomerular capillary walls (Figure 2C). Immunofluorescence of IgG subtypes in paraffin sections showed that IgG1 weak positive (Figure 2D), IgG2 and IgG3 negative (Figures 2E,F), IgG4 positive deposit in the GBM (Figure 2G). Electron microscopy indicated that massive electron dense deposition in the glomerular subepithelial and GBM, and extensive fusion of epithelial podocytes (Figure 3A). It also showed the absence of cellular broadening in the GBM and the mesangial area of the glomeruli, along with disorderly deposits of fibrous material (Figures 3B,C). The renal interstitium had the same characteristic deposition of fibrous material (Figure 3B).

Based on the clinical indicators and pathological findings, this patient was finally diagnosed with NS, with the pathology type being IMN with AL type amyloid nephropathy. The

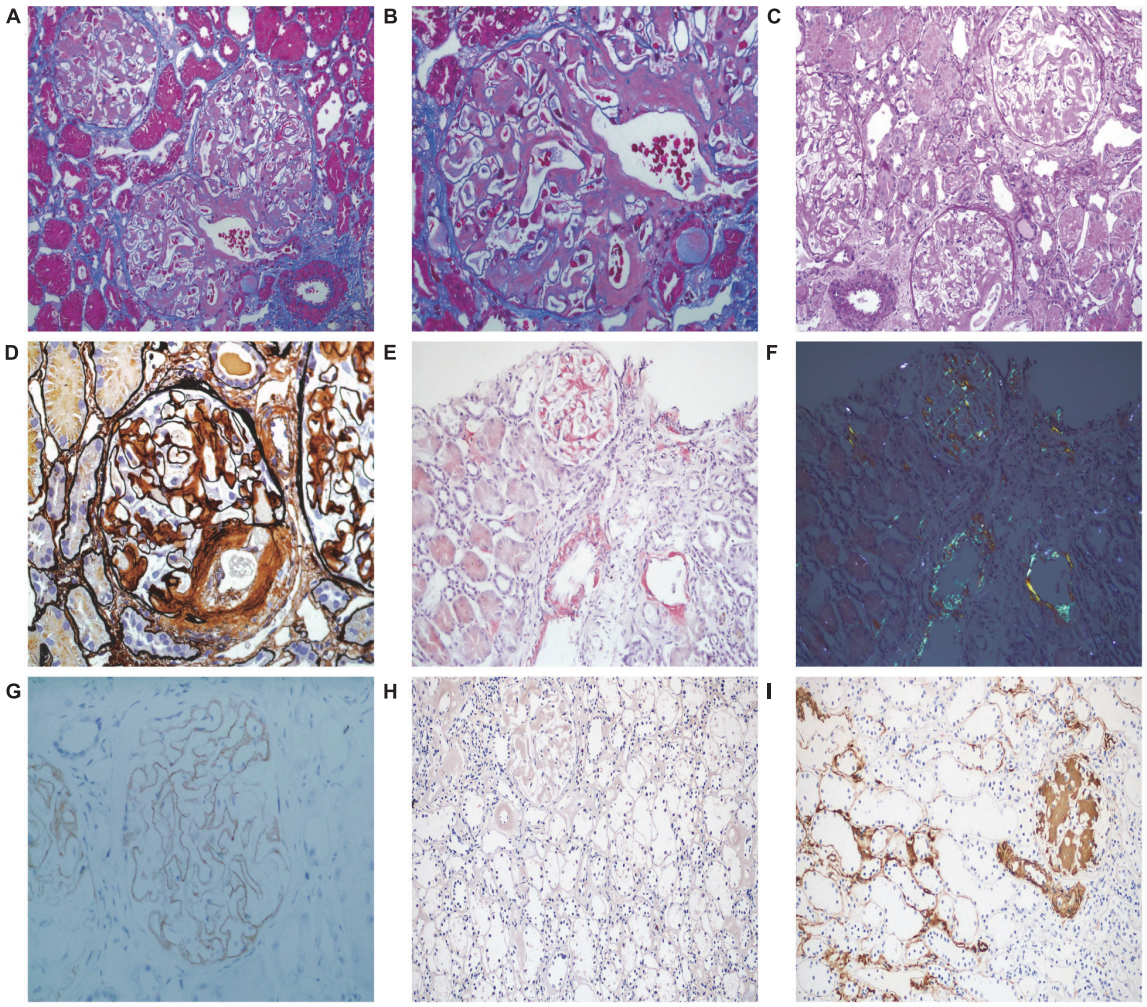

FIGURE 1
Pathological features of light microscopy and immunohistochemistry. **(A,B)** Small amounts of erythrophilin were deposited under epithelial cells, and vacuolar degeneration of renal tubular epithelial cells (Masson staining, 200 × and 400×, respectively). **(C)** Deposition of eosinophilic homogeneous unstructured material in the mesangial region, capillary wall, local interstitium, and some arteriolar walls (PAS staining, 200×). **(D)** Diffused mesangial broadening, with the basement membrane thickened segmentally, no absence of spike formation and no eyelash-like changes in the glomerular basement membrane (PASM staining, 400×). **(E)** Positive staining of Congo red of glomeruli, partial arteriole walls, and local interstitium (Congo red staining, 200×). **(F)** Pathological apple-green birefringence under cross-polarized light (200×). **(G)** Fine granular deposition of phospholipase A2 receptor along the capillary walls (immunohistochemistry, 400×). **(H)** Amyloid-associated protein was negative in the mesangial area of the glomeruli and arteriolar wall, as well as in the focal renal interstitium (immunohistochemistry, 200×). **(I)** Amyloid-associated protein staining positive control (immunohistochemistry, 200×).

patient also had hyperuricemia, peritoneal effusion, and hypothyroidism. The chest CT showed slight inflammatory changes, but the patient had no respiratory tract infection symptoms, and the infection-related indicators were normal. Therefore, we considered the patient did not have infection or chronic inflammation. The patient had hypotension, but no palpitation. Examination revealed sinus rhythm and normal cardiac structure and blood flow. Therefore, we considered the hypotension might be related to amyloidosis. The patient had a large amount of ascites, but the liver function of the patient was normal. Hypoproteinemia caused by NS can cause edema, and the decrease in daily urine volume will aggravate it. Therefore, we believed that the cause of ascites was leakage due to hypoproteinemia caused by NS.

Treatment was primarily aimed at preventing the complications of NS. While hospitalized, the patient was treated with statins to control blood lipid concentrations, aspirin as an anticoagulant, and intermittent intravenous supplementation of human serum albumin and diuretics to promote urination and reduce edema. He was also treated with thyroxine to improve his thyroid gland hypofunction. The patient was advised to go to the Hematology Department for further bone marrow biopsy and to determine the treatment plan for amyloidosis, but he refused for financial reasons. After

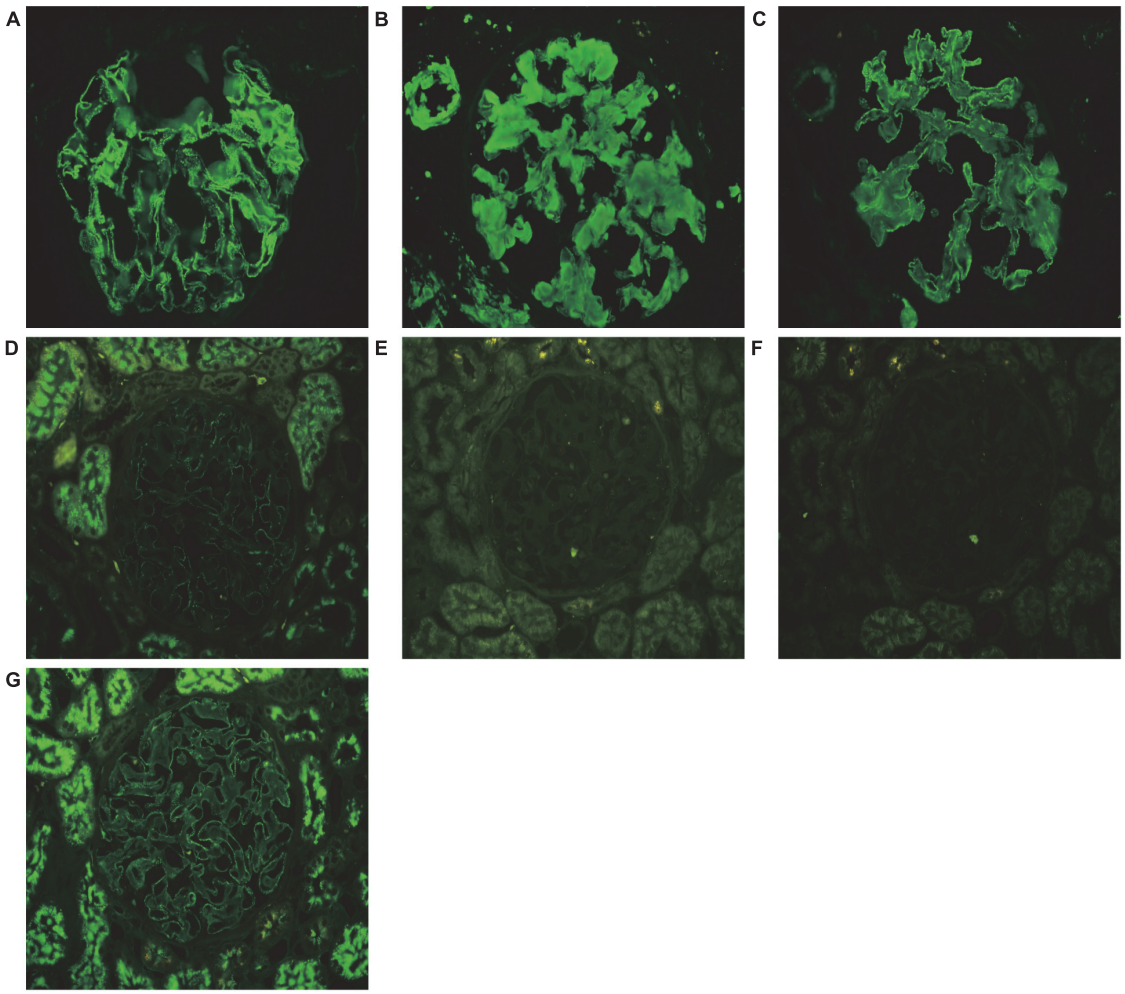

FIGURE 2
Pathological features of immunofluorescence. **(A)** Granular deposition of IgG (+++) along the glomerular capillary walls (immunofluorescence, 400×). **(B)** Deposits of λ (++) along the arterioles, mesangial glomeruli, and capillary walls (immunofluorescence, 400×). **(C)** Deposits of κ (+) along the glomerular capillary walls (immunofluorescence, 400×). **(D)** Weak positive of IgG1 deposition in the glomerular basement membrane (immunofluorescence, 400×). **(E)** IgG2 was negative in the glomerular basement membrane (immunofluorescence, 400×). **(F)** IgG3 was negative in the glomerular basement membrane (immunofluorescence, 400×). **(G)** Positive of IgG4 deposition in the glomerular basement membrane (immunofluorescence, 400×). **(A–C)** Show the immunofluorescence of frozen section, and **(D–G)** show the immunofluorescence of paraffin section.

discharge on May 5, 2018, the patient was not regularly followed up in our hospital, and was lost to follow-up.

Discussion

This patient was a middle-aged male with chronic onset of disease. He had no history of other medical diseases. Clinical manifestations included NS and mildly elevated serum creatinine. His weight had decreased significantly in 1 year. Besides renal damage, the patient also had hypotension, which made us suspect he was likely to have secondary NS. Proteinuria classification showed a significant increase in urine λ-light chain and a concomitant increase in serum free-λ chain. Renal puncture biopsy showed the glomeruli, some arteriolar walls, and the local interstitium were positively stained with Congo red, and pathological apple-green birefringence was produced under cross-polarized light. Immunofluorescence suggested strongly positive deposition of λ chain along the small arteries, glomerular mesangial area and capillary walls, but κ chain deposition was weak. IgG, IgM were deposited in the glomerular capillary wall in granular form, but not in the area of amyloid deposition, and IgA was (±), so we did not consider the deposition of heavy chain in the deposition area of amyloid. Immunohistochemistry showed that AA was negative, so AA amyloidosis could be ruled out. Electron microscopy showed an absence of cellular broadening in the mesangial region and

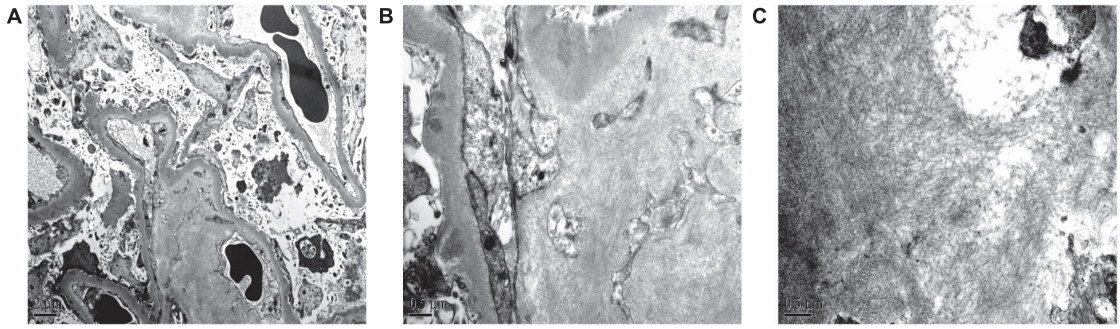

FIGURE 3
Renal pathological features of electron microscopy. **(A)** Massive electron dense deposition in the subepithelial and basement membranes, and extensive fusion of epithelial podocytes (electron microscopy, 6,000×). **(B,C)** Scattered fibrous deposits in the mesangial region, basement membrane, and interstitium of the kidney (electron microscopy, 25,000× and 30,000×, respectively).

basement membrane of the glomeruli, with scattered fibrous deposits in the mesangial region and renal interstitium. Renal pathological examination indicated that the deposition area of amyloid was consistent with the deposition area of λ. The above pathological changes suggested amyloid nephropathy, and the subtype was AL type.

However, to our surprise, the renal pathology also had the characteristics of MN. Light microscopy showed segmental thickening of the GBM. Immunofluorescence showed granular deposition of IgG along the glomerular capillary walls. Electron microscopy showed a large amount of electron dense deposits in the subepithelial membrane and GBM, and extensive fusion of epithelial podocytes. These typical pathology findings suggest that the patient's renal pathology can be diagnosed as MN. In order to further clarify whether the patient is an IMN, we tested the serum anti-PLA2R antibody IgG and the result was negative. Therefore, we further detected PLA2R in renal biopsies. Immunohistochemistry showed that PLA2R was positively expressed along the fine particle deposition of capillary walls. Based on the medical history and clinical auxiliary examination, diagnoses of secondary MN were excluded. The above information supported the patient with IMN.

Amyloidosis is a group of diseases caused by the deposition of amyloid protein in the extracellular matrix, resulting in tissue and organ damage at the deposition site. The kidneys are most frequently involved in systemic amyloidosis, with renal amyloidosis in most patients due to immune globulin (5). AL type amyloidosis is the most common type of systemic amyloidosis and has been associated with the abnormal proliferation of monoclonal plasma cells, as well as with lymphoproliferative diseases (6). According to the precursor proteins that form amyloid fibroids, amyloidosis can be divided into primary systemic amyloidosis such as AL type and amyloid immunoglobulin heavy chain type, secondary systemic amyloidosis also known as AA type, hereditary amyloidosis, and other main types (7). Patients with amyloidosis are staged using the Mayo Clinic staging system (8).

The incidence of amyloidosis is uncertain, but AL amyloidosis is thought to have an annual incidence of 6–10 per million persons in the United Kingdom and United States (7). Although the incidence rate in China is undetermined, domestic renal biopsy data have found that AL amyloidosis is present in about 3.63% of patients with secondary kidney disease (9). In developed countries, approximately 75–80% of all MN are idiopathic, the remaining 20–25% are secondary to different conditions (10, 11). In recent years, in China, the incidence rate of MN has also shown a trend of gradually increasing (9). But MN with amyloid nephropathy is rare. MN complicated with renal amyloidosis has been reported abroad, but most of them are secondary MN complicated with amyloidosis, such as chronic lymphocytic leukemia, rheumatoid arthritis and Waldenström's macroglobulinemia, which may lead to the deposition of immune complexes in glomeruli caused by antigen exposure (12–14). Four cases of amyloid nephropathy complicated with IMN have been reported in China (15–18). The renal amyloidosis and IMN mentioned in the above four cases are considered to be separate diseases without other secondary factors.

Our case has its own characteristics compared with the above-mentioned reports of renal amyloidosis with IMN. In terms of clinical indicators, all the above cases (except one case that was not tested) were positive for serum anti-PLA2R antibody. But in our case, the patient's serum anti-PLA2R antibodies was negative, kidney tissue PLA2R antigen was positive, the reasons might be as follows: (1) 70% of patients with IMN had positive circulating anti-PLA2R autoantibodies (4). Circulating serum anti-PLA2R antibodies may be negative in some situation, such as when the time from the onset of MN to renal biopsy is too long, during disease immune remission, when the affinity between antigen and antibody is strong, or when some other reasons lead to fast antibody clearance (19). (2) It may be related to the imperfect detection technology. (3) This patient had amyloid nephropathy, but it was not excluded that abnormal light chain synthesis by plasma cells affected the

production of antibodies against PLA2R by B cells. When the serum anti-PLA2R antibodies is negative, the PLA2R antigen can still be detected in the kidney, indicating that it has a higher sensitivity. Many studies in recent years have shown that serum anti-PLA2R antibodies were closely related to IMN disease activity, and suggested that the change of the anti-PLA2R antibody level in IMN patients is closely related to the status of IMN (20–22). According to the latest KIDIGO guidelines (23), a kidney biopsy may not be needed in anti-PLA2R-positive patients with a low risk of disease progression and/or a high risk of biopsy-related morbidity. In serum anti-PLA2R antibody negative patients, a kidney biopsy is needed to diagnose MN. In such patients, it is important to look at whether PLA2R staining is present in the glomeruli, because this will allow identification of patients with PLA2R-associated MN.

In terms of renal pathology, IMN in all of the above cases (except one case not described) was characterized by spike formation. But in our case, the pathological Periodic acid-silver methenamine staining did not show the formation of spike due to deposition of immune complexes and lash-like structural changes due to amyloid of the GBM. We consider the absence of spike formation is related to the simultaneous deposition of amyloid in GBM. Amyloid is mainly deposited in the mesangial region of the glomeruli and the basement membrane of capillaries, the basement membrane of renal tubules and the walls of arterioles. In severe cases, amyloid can be deposited in the renal interstitium. At the early stage, the GBM was slightly thickened, with Periodic acid-silver methenamine staining showing segmental eyelash structures as a result of amyloid deposition under the GBM epithelium (24, 25), it can be easily confused with MN. According to the characteristics of amyloid protein under electron microscopy and the immunofluorescence characteristics of MN, the two diseases could be distinguished. Glomerular damage in amyloidosis usually occurs without GBM thickening. Segmental elongated "spicules" extending from the GBM are a common feature (5, 26). There were cases reported that non-branching fibrils could focally appeared to disrupt the GBM and protrude into Bowman space into the cytoplasm of the podocytes. Podocyte foot processes were extensively effaced. Pathological findings of these above two cases showed amyloid nephropathy with obvious epithelial hyperplasia and glomerular collapse with clinical manifestations of acute kidney injury and NS (27). There is no known case of amyloidosis leading to exposure of GBM antigens and antibodies production leading to MN. It is not clear whether IMN is caused by antigen exposure after amyloid deposition in this case. However, considering the absence of disruption of GBM due to amyloidosis in this case, and in combination with other pathological findings, it is unlikely that IMN is caused by amyloidosis, we considered renal amyloidosis and MN as independent of each other.

The diagnostic criteria of MN and the diagnosis and treatment of AL amyloidosis criteria have been defined according to the KDIGO guidelines published in 2020 (23) and the guidelines for the diagnosis and treatment of AL amyloidosis developed by the Standards Committee of the British Society of Hematology (28). B-cell anomalies play a role in the pathogenesis of MN. Selective B-cell removal by rituximab appears to be a more promising treatment compared with cyclophosphamide, which has the characteristic of non-selective B-cell depletion (29). 2020 KDIGO guidelines for glomerulonephritis suggest that (23), for patients with MN and at least one risk factor for disease progression, using rituximab or cyclophosphamide and steroids for six months is recommended. Rituximab has become a first-line treatment in the treatment of MN. The treatment of patients with AL amyloidosis is based on the treatment of multiple myeloma, but there is no standard treatment for the former. Localized amyloidosis can be treated by local resection or radiation (28). Other treatments can include autologous peripheral blood stem cell transplantation; anti-plasma cell therapy, such as proteasome inhibitor, monoclonal antibodies, immunomodulatory drugs, and alkylating agents; anti-amyloid filament therapy; and supportive therapy (6, 28, 30, 31). Daratumumab is a humanized monoclonal IgG1-κ antibody that targets the plasma cell surface CD38 antigen (6, 30). The ANDROMEDA trial showed that subcutaneous injection of cyclophosphamide, bortezomib, dexamethasone combined with daratumumab improved overall response rate, organ response rate, and progression-free survival time of major organs (32). Doxycycline was found to interfere with amyloid fibril formation in a transgenic mouse model of AL amyloidosis (33), suggesting that doxycycline in combination with other agents can be used during the first year after diagnosis to treat patients with AL amyloidosis who are or are not transplant eligible (6, 30).

CD20 or CD38 may be the main source of autoantibodies in IMN. For patients with high anti-PLA2R antibody titers, reducing CD20/38 may be an effective intervention (34, 35). At the same time, CD38 is also an ideal target for the treatment of amyloidosis (36). A multinational research team from the United States and Belgium published the latest research on felzartamab, which proved it can effectively reduce the anti-PLA2R antibody titer of patients with MN, and felzartamab, as an anti-CD38 monoclonal antibody, has good therapeutic potential in the treatment of light chain amyloidosis (37). This may provide a new therapeutic prospect for IMN with amyloid nephropathy patients.

Conclusion

The combination of MN and amyloidosis is rare. This study described a patient with IMN accompanied with amyloid nephropathy. This case has some shortcomings. The patient did not undergo bone marrow biopsy and accept drug treatment in

our hospital. He did not return to our hospital for follow-up and he was lost to follow-up, which made the case incomplete. However, we hope to deepen our understanding of this disease through the sharing of this case. The detection of serum anti-PLA2R antibody and glomerular PLA2R antigen is helpful for the diagnosis of IMN. In addition to light microscopy, Congo red staining and immunofluorescence examination, since early AL renal amyloidosis may not have obvious light microscopy and immunopathological features, electron microscopy is very important for the diagnosis of renal amyloidosis. For cases with unclear classification, immunohistochemistry, immunoelectron microscopy, mass spectrometry and even genetic testing can be used if necessary.

Data availability statement

The original contributions presented in this 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.

Author contributions

YW, XW, and WS collected, analyzed, and reviewed the clinical data of the patient. JY and SW performed and diagnosed the histological examinations of the kidney biopsy sample. WS and ZX suggested the revisions of the manuscript. All authors read and approved the final manuscript.

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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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Case report: Successful outcome of treatment using rituximab in an adult patient with refractory minimal change disease and β-thalassemia complicating autoimmune hemolytic anemia

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Minimal change disease (MCD) is one of the common causes of idiopathic nephrotic syndrome (INS), accounting for 10–20% of INS in adults. Glucocorticoids are the most commonly used and effective drugs in the treatment of MCD, but there is still a proportion of adult patients with MCD who are characterized by glucocorticoid resistance, glucocorticoid dependence, and frequent relapse, which are defined as refractory nephrotic syndrome. Glucocorticoid combination with immunosuppressants is frequently used in patients with refractory nephrotic syndrome, and patients concerned about adverse effects caused by long-term high-dose glucocorticoid therapy. Recent studies have suggested that Rituximab (RTX), a chimeric monoclonal antibody targeted against the pan-B-cell marker CD20, combined with a small or medium dose of glucocorticoid has a beneficial effect with less adverse effects on adult patients with refractory MCD. β-thalassemia is an inherited hemoglobulin disorder caused by the mutation of genes that encode β-globin and results in ineffective erythropoiesis. We here report a case of an adult patient with refractory MCD complicated with β-thalassemia minor accompanied by autoimmune hemolytic anemia (AIHA). MCD relapsed several times despite treatment using glucocorticoid combined with or without different immunosuppressive agent regimens. The β-thalassemia minor was caused by heterozygosity for a 4-base deletion mutation [codons 41/42 (−TTCT) BETA^0] of the β-globin gene. After the administration of RTX, MCD achieved clinical complete remission, and the

anemia due to mild β-thalassemia recovered to normal as well. The disease situation remained stable during 36 months of follow-up. These findings suggest that RTX may contribute to the improvement of refractory MCD and anemia in β-thalassemia minor accompanied by AIHA.

KEYWORDS

refractory nephrotic syndrome, minimal change disease, β-thalassemia, rituximab, autoimmune hemolytic anemia

Introduction

Minimal change disease (MCD) is one of the common causes of idiopathic nephrotic syndrome (INS) in adults, with the use of glucocorticoids being the mainstay. Although the use of glucocorticoids is generally effective in the treatment of adult patients with MCD, there are many challenges in clinical practice such as frequent relapse of kidney disease, glucocorticoid resistance, severe adverse effects induced by glucocorticoids, etc. (1). MCD is a glomerular disease characterized by podocyte injury. The pathological features of the kidney generally show normal glomerular structure under the light microscope and diffuse effacement of the podocyte foot process under the scanning electron microscope (2, 3). The response rate of adult patients with MCD to glucocorticoid treatment has been reported approximately 75% (4). While long-term glucocorticoid treatment can cause adverse effects even life-threatening outcomes. With Rituximab (RTX), a chimeric monoclonal antibody targeted against the pan-B-cell marker CD20, successful application in many immune-mediated proteinuric glomerular diseases such as primary membranous nephropathy (3), patients with glucocorticoid-dependent or glucocorticoid-resistant MCD have been tried to treat using RTX and promising improvement in these patients have been observed (3, 5). The mechanism of action of RTX on the MCD may be mediated by the depletion of $CD20^+$ B lymphocytes and reconstruction of abnormal Th17/Treg cell balance (6).

β-thalassemia is one of the most common inherited HGB diseases in the red blood cells, that is caused by abnormal β-globin genes (*HBB*) and HGB synthesis (7). Depending on the affected numbers of *HBB* and the severity of the anemia, β-thalassemia has been classified into three types consisting of the minor (trait), intermedia, and major types. Patients with heterozygous β thalassemia, namely minor type, usually present no symptoms of anemia except complicating the autoimmune hemolytic anemia (AIHA) (8). Here, we report an adult female patient with refractory MCD and β-thalassemia complicating AIHA who has been treated with RTX, both of the symptoms of kidney disease and anemia have been greatly improved and reached complete remission, and remained stable during 36 months of follow-up. These findings suggest that the RTX treatment may be a potential therapeutic strategy for adult refractory MCD and/or AIHA.

Case presentation

A 22-year-old Chinese woman came to the hospital due to persistent fatigue in 2016. The complete blood count (CBC) results showed normocytic normochromic anemia and hemoglobin (HGB) levels were 89 g/L. She was diagnosed with β-thalassemia without specific treatment for anemia at that time. In the same year, she was referred to our hospital due to sudden peripheral edema in both lower legs and a recent 2-kg increase in body weight, proteinuria, and hypoalbuminemia, and she was diagnosed with nephrotic syndrome. Her past medical history was not significant. She had regular menstruation and normal eating habits. The findings of the physical examination showed normal blood pressure with 120/70 mmHg, mild anemia, mild pitting edema of both lower limbs, and no rash or arthralgia. Laboratory tests results showed that 2 + of urine protein, hypoalbuminemia (28 g/L), normal range of serum creatinine levels; normocytic normochromic mild anemia, positive Coombs test, reticulocytosis, without any positive signs on the liver, spleen and systemic superficial lymph nodes. The level of serum lactate dehydrogenase (LDH) was normal (233 U/L, normal range in our hospital: 109–245 U/L). The patient was further examined excluding common secondary causes leading to anemia such as systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), hepatitis B virus infection, hepatitis C virus infection, and human immunodeficiency virus (HIV) infection, paroxysmal nocturnal hemoglobinuria, etc. A renal biopsy was performed to pathologically analyze the cause of the nephrotic syndrome which showed the MCD (**Figure 1**).

To further investigate the underlying cause of anemia, after discussion with the patient and obtaining her consent, the peripheral mononuclear cells were isolated from the blood for a gene test described as in our previous study (9). In brief, Genomic DNA was extracted from peripheral blood samples using the blood genomic DNA Extraction

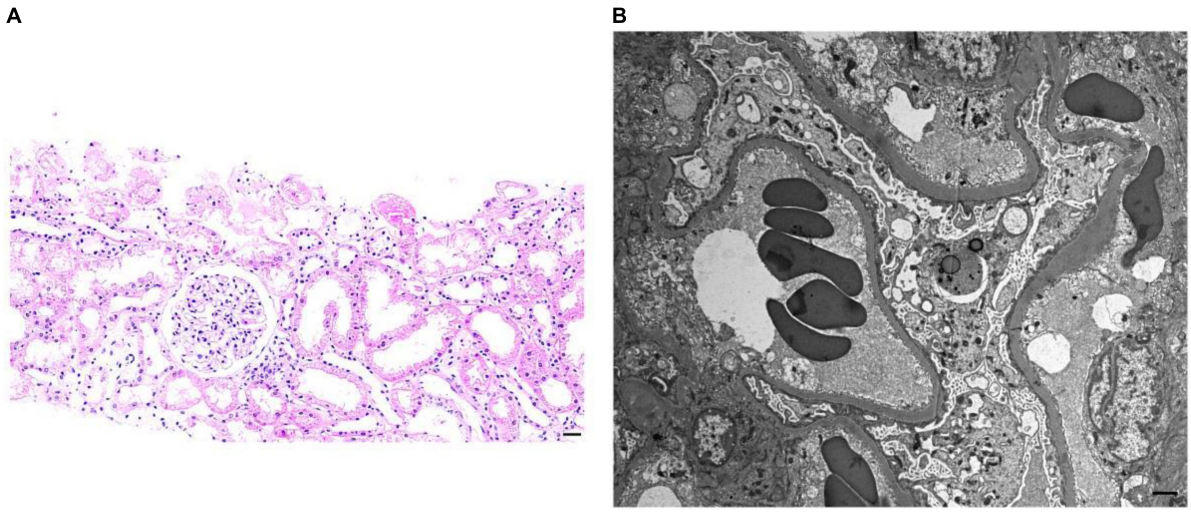

FIGURE 1
Representative images of light microscopy and transmission electron microscopy (temtem) from the kidney biopsy of the patient.
(A) Hematoxylin and eosin staining showed no significant changes in glomeruli, renal interstitium, and renal tubules (scale bar: 100 μm).
(B) Representative TEM showed the diffuse foot process effacement of podocytes, and no electron-dense deposition in the subepithelial, subendothelial, and mesangial compartments was detected (scale bar: 1 μm).

Kit and the Thermo Scientific KingFisher Flex magnetic Bead Purification System. The α-globin genes (*HBA*) and *HBB* were detected by high-throughput sequencing. Four deletion types of alpha-thalassemia ($--^{SEA}$, $-\alpha^{3.7}$, $-\alpha^{4.2}$, and $--^{THAI}$) and three deletion types of β-thalassemia [Chinese Ggamma (Agammadeltabeta)0, SEA-HPFH, Taiwan type] were detected by gap-PCR. Meanwhile, more than 153 mutation types of α-thalassemia and more than 348 mutation types of β-thalassemia were detected as well. PCR amplification was performed using TaKaRa PCR amplification reagent 2 × GC Buffer I and TaKaRa Taq^{TM} Hot Start Version (BGI Diagnosis Co., Ltd., Shenzhen, China). Analysis results revealed heterozygosity for Codons 41/42 (−TTCT) BETA^0 of the β-globin gene (**Figure 2**). The patient had no siblings. Her parents presented normal HGB levels and declined the request for the gene test.

According to the renal histopathological changes, treatment with oral prednisolone acetate at a dose of 40 mg/day was initiated, and clinical complete remission for the nephrotic syndrome was achieved after 4 weeks of treatment based on the criteria recommended by The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases in 2021 (10). However, kidney disease recurred during the gradual taper of the glucocorticoid dose. Given that, the treatment regimen was changed to prednisolone acetate at a dose of 20 mg/day in combination with mycophenolate mofetil (MMF) at a dose of 1.5 g/day by mouth to control the kidney disease, during which the levels of 24-h urinary protein excretion decreased. In March 2017, kidney disease recurred without the defined causes. The therapeutic regimen was adjusted to prednisolone acetate at a dose of 10 mg/day in combination with the calcineurin inhibitor tacrolimus (FK506) at a dose of 2 mg/day, the trough concentration of tacrolimus was maintained at 4.2 ng/ml. After 1 month of treatment, partial clinical remission of nephrotic syndrome was achieved. However, kidney disease recurred again after 1 year without any defined cause, and the treatment regimen was changed to prednisolone acetate combined with oral cyclophosphamide by mouth. The MCD relapsed 5 times totally during the dose taper of prednisolone acetate. After discussion with the patient, the therapeutic regimen was adjusted to multi-target treatment using prednisolone acetate at a dose of 25 mg/day, MMF, and FK506. Partial remission of the nephrotic syndrome was reached with a trough level of FK506 of 2.7–6.9 ng/ml and a cumulative dose of 5.8 g for cyclophosphamide (**Figure 3**). Of note, the HGB levels for this patient kept low levels without any change during the treatment. There was no gastrointestinal bleeding or increased menstrual volume. The results of ferritin and transferrin saturation excluded iron deficiency anemia. She has no allotriophagia habit and no past medical history of blood transfusion. The results of kidney function showed normal. The anemia caused by chronic loss of red blood cells, impairment of kidney function, and side effects of drugs were excluded. The result of the CBC showed no significant abnormalities in white blood cell count and platelet count. The Coombs test was still positive. The request for a bone marrow aspiration or biopsy was declined by the patient. These findings revealed that the mild anemia may be caused by β-thalassemia minor combined with autoimmune hemolysis.

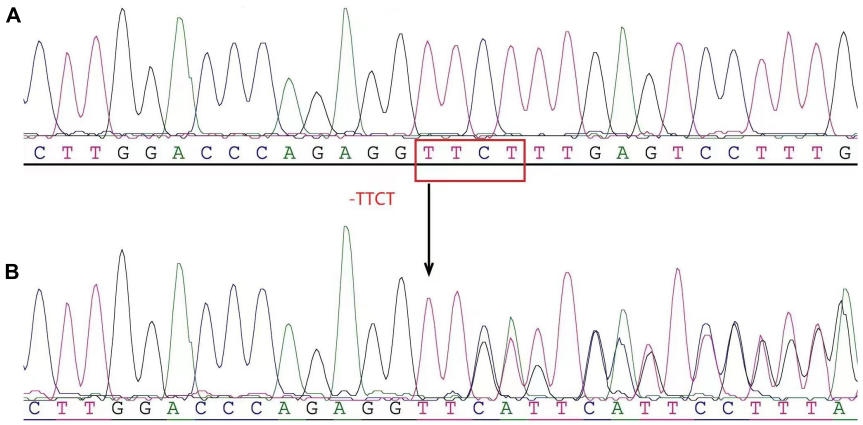

FIGURE 2
The heterozygosity for the 4-base deletion mutation [codons 41/42 (−ttct) bETa^0] of the β-globin gene (*hbb*) was determined by high-throughput gene sequencing. **(A)** Normal control reference sequence. **(B)** Patient. The arrows indicated the site of the deletion mutation of the β-globin gene.

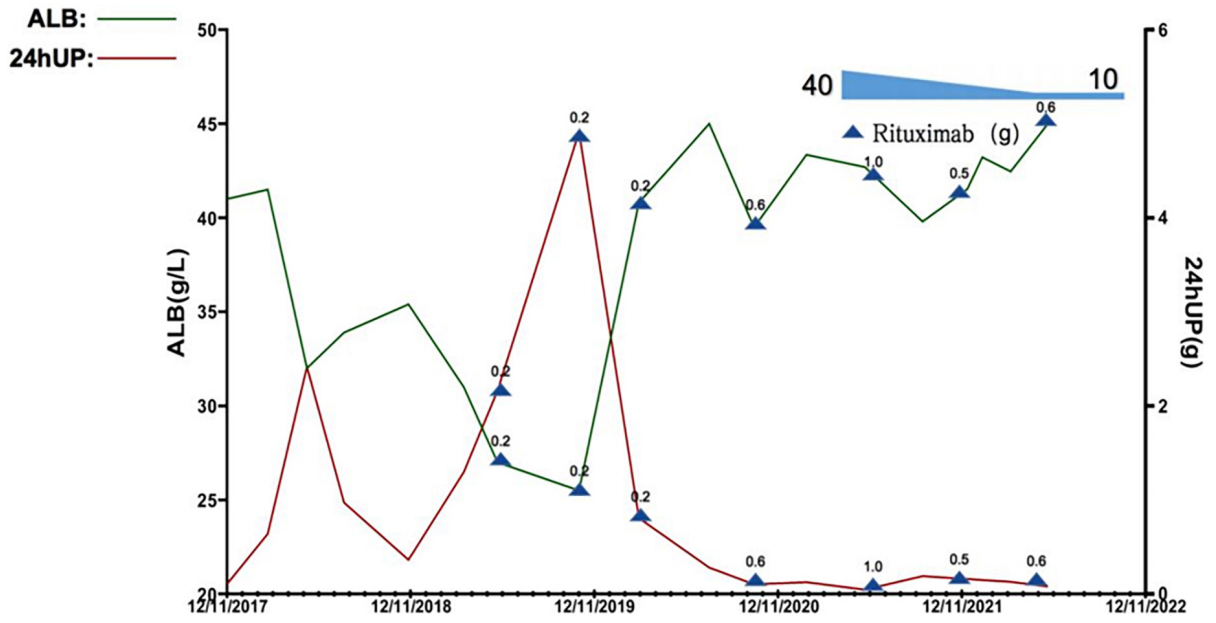

FIGURE 3
Quantification in levels of plasma albumin (alb) and 24-h urinary protein excretion (24hUP) of this patient during the observational period. 0.2, 0.5, 0.6, and 1.0 denote the dose of rituximab used at this timepoint (g, gram).

The adverse effects associated with long-time use of glucocorticoids including skin acne, and osteoporosis emerged in this patient. Considering the patient's refractory MCD and β-thalassemia minor complicating with AIHA, detailed discussions regarding the diseases and the adverse effects of long-term use of glucocorticoid and immunosuppressive agents were conducted with the patient. With the permission of the patient, the CD20$^+$ B-cell depletion biological agent RTX combined with prednisolone acetate at the dose of 25 mg/day plus FK506 at a dose of 0.5 mg twice a day was administered starting from September 2019.

The RTX dose and schedule used in this patient were guided by the serum CD19$^+$ B lymphocyte counts, immunological status, evaluation of potential infection risk, and the response to the RTX treatment. The cut-off of serum CD19$^+$ B lymphocyte counts was 5/μl. Eight doses of RTX were given as follows, 200 mg on September 2019, 500 mg on November 2019, 200 mg on March 2020, 500 mg on July 2020, 600 mg on January 2021, 1,000 mg on June 2021, 500 mg on Dec 2021, and

600 mg on June 2022. The glucocorticoid has been tapered and withdrawn in the end. The serum $CD19^+$ B lymphocyte counts were significantly decreased. The parameters associated with refractory MCD including increased 24-h urine protein excretion and hypoalbuminemia, and anemia significantly improved 6 months after treatment, the Coombs test turned negative. The serum $CD19^+$ B lymphocyte counts gradually reconstructed and returned to normal after 4∼5 months of RTX withdrawal. During the 36-month follow-up observational period, clinical complete remission of refractory MCD and normal blood HGB levels remained stable (**Figures 3**, **4**).

Discussion

Here we reported a case of a young Chinese woman with refractory MCD and β-thalassemia minor complicating AIH. According to the 2021 KDIGO guideline for glomerular disease, adequate glucocorticoids are recommended for the adult patient with MCD treatment, combined immunosuppressive agents are recommended if necessary (10). The patient was treated with a series of recommended therapeutical regimens for refractory MCD using glucocorticoids combined with other immunosuppressive agents. The clinical outcome was not satisfactory, whereas the adverse effects of the drugs emerged. Long-term use of glucocorticoids in the patient can cause unavoidable adverse effects, mainly manifested as infection, skin acne, osteoporosis, increased psychological burden, and decreased quality of life (9). In order to reduce the adverse effects caused by glucocorticoids and other immunosuppressive agents, and favor the recovery of refractory MCD, the RTX was administered to this patient. Notably, both kidney disease and anemia caused by β-thalassemia minor complicating AIH reached complete remission and remained stable during the 36-month follow-up observational period.

The pathogenesis of MCD remains elusive although the understanding of the underlying pathogenic mechanisms for MCD has recently made a tremendous leap. Studies indicate that the pathogenesis of MCD is closely related to immune disorders, and may be affected by genetic factors and environmental factors (3, 11). Activation of T cells plays an important role in the occurrence and development of MCD. Burgeoning studies have shown that the involvement of B cells in activating T cells may also play a role in the pathogenesis of MCD. In addition to the synthesis of specific antibodies stimulated by antigens, B cells are also involved in antigen presentation and costimulatory signals and secrete cytokines to regulate the differentiation of T cells (12). Recently, the use of RTX in children and adults with refractory nephrotic syndrome has achieved promising efficacy, which further suggests that B cells may play an important role in the pathogenesis of MCD (5). RTX is a chimeric monoclonal antibody targeted against the pan-B-cell marker CD20 molecule with mouse variable and human constant region. By binding to CD20 molecules on the surface of B cells, RTX causes rapid depletion of $CD20^+$ B cells through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and induction of apoptosis (13). Because B cells can activate the antigen presentation function of T helper cells (14), the depletion of B cells regulates the immunological function of T cells and reduces the secretion of various cytokines and circulating factors. The underlying mechanism of RTX on the inhibition of B cell growth or promotion of B cell apoptosis may be mediated by its activation of protein kinase and phospholipase Cγ (15). Additionally, RTX can enhance CTLA4 (Cytotoxic T-lymphocyte Associated Protein 4) production by regulatory T cells (Treg), thereby inhibiting CD80 activation and signaling pathways between antigen-presenting cells and T cells, which favors the reconstruction of immune disorders in glomerulus and reduction of proteinuria (11). Recent small-size sample studies have shown that RTX can rapidly mitigate the nephrotic syndrome in adult MCD and maintain a longer remission (11, 16). These findings suggest that RTX may be a safe and effective alternative to glucocorticoids and other immunosuppressive agents in patients with a long history of relapsing refractory MCD. The adult female patient with refractory MCD reported here responded very well to eight times RTX treatment as needed and no adverse events were observed during the whole 36-month follow-up observational period. Similar studies using more than two doses of RTX for the successful treatment of adult patients with frequently relapsing MCD have been recently reported (5, 17). The mechanism of the RTX treatment favoring the remission of MCD remains quite unclear. A 2022 study reported that the serum antibodies against nephrin, an important podocyte-specific protein, have been discovered in some children and adult patients with MCD, the anti-nephrin antibodies presented positive during the active phase and negative during the remission phase after treatment. Meanwhile, confocal microscopy showed the co-localization of immunoglobulin G (IgG) and nephrin in the glomerular podocytes (18). These findings suggest that B cell-associated humoral immunity is also possibly involved in the pathogenesis of MCD. The glomerular podocyte injury is the predominant pathological feature of MCD, which cause the dysfunction of the integrity of the glomerular filtration barrier (3). Nephrin is a 180 KD transmembrane junction protein specifically located on slit diaphragm membranes between adjacent podocyte foot processes, which is a key protein involved in maintaining the podocyte cytoskeletal structure and integrity of the glomerular filtration barrier (19). The recovery of impaired nephrin, either loss or translocation, to normal may serve as a specific marker predicting clinical remission of MCD (20). Recent reports showed that RTX could specifically increase the expression of SMPDL3b (Sphingomyelin phosphodiesterase acid-like 3B) in podocytes, thereby stabilizing the cytoskeleton of podocytes, reducing podocyte apoptosis, and protecting podocyte function (21). Recent studies have shown that RTX can substantially

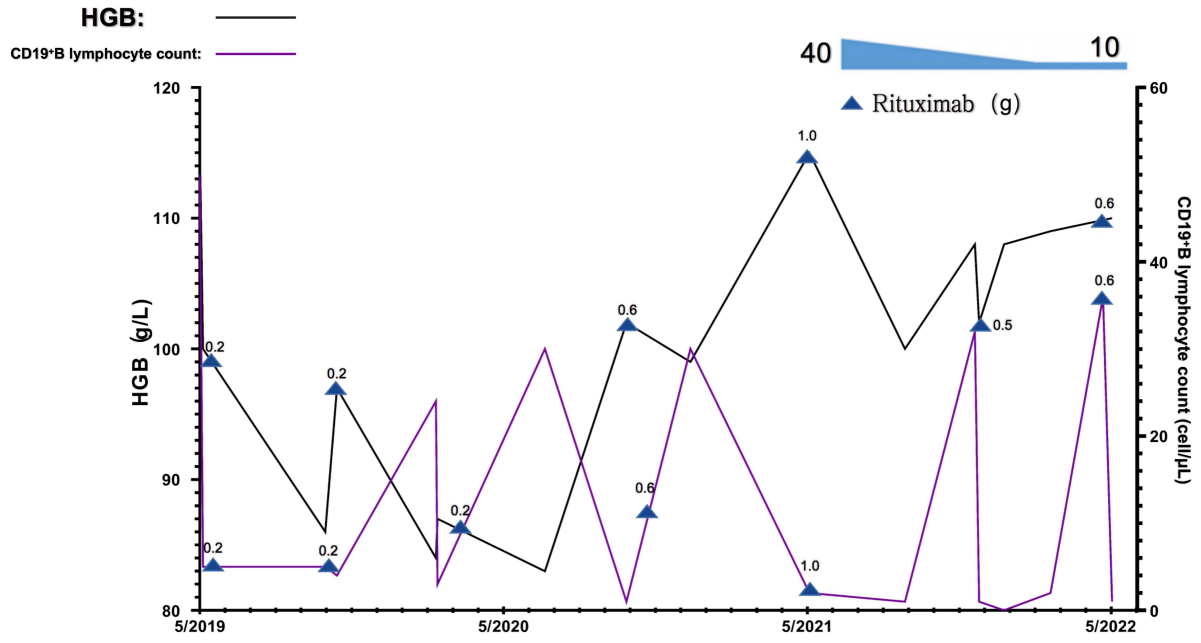

FIGURE 4
Changes in blood hemoglobin (hgb) levels and CD19^{+}B lymphocyte counts of this patient during the observational period. 0.2, 0.5, 0.6, and 1.0 denote the dose of rituximab used at this timepoint g, gram.

increase the remission rate of MCD in adults with refractory nephrotic syndrome to 70.4% and higher, shorten the time reaching remission to 1–2 months, significantly reduce the dose of glucocorticoid use, and greatly alleviate the recurrence rate of MCD (22), Nevertheless, more convincing evidence and data are required to understand the underlying immune pathogenesis of MCD and efficacy of RTX on MCD.

The patient reported in this study also presented mild anemia caused by β-thalassemia minor complicating with AIHA. The genetic testing result revealed compound heterozygosity for a 4-base deletion mutation [Codons 41/42 (−TTCT) beta^{0}] in the HGB β gene *HBB*. The prevalence of thalassemia was 0.46 per 1,000 cases (23). In a recent study of prenatal diagnosis of α-thalassemia and β-thalassemia in 3,049 families in China, the most common mutation for β-thalassemia was the mutation of Codons 41/42, which accounted for 30.27% (24). A previous study reported the rate of patients with β-thalassemia co-existence of autoantibodies or alloantibodies was 38.9% (25). In some patients with β-thalassemia, anti-erythrocyte autoantibodies are present, making the direct antiglobulin test (DAT) positive. In the past, there is no specific treatment regimen recommended for such mild anemia with β-thalassemia patients with autoimmune hemolysis, but the persistent anemia leads to potential harm to the functions of organs and a significant decline in the quality of life of patients. The confirmative diagnosis of β-thalassemia depends on gene tests and DNA analysis. Genetic analysis showed that the patient had compound heterozygosity for the Codons 41/42 (−TTCT) Beta^{0} mutation, which not only resulted in structural abnormality of HGB but also caused mild anemia. To our knowledge by reviewing the published papers available, it is the first time to report the efficacy of RTX treatment on an adult patient with refractory MCD, who also has the β-thalassemia complicated with AIHA caused by Codons 41/42 (−TTCT) BETA^{0} in the *HBB*. However, there is no evidence to support whether the variant of the Codons 41/42 (−TTCT) BETA^{0} in *HBB* of this patient is an inherited or sporadic variation as she has no siblings and her parents refused genetic testing. The favorable effect of RTX on the improvement of anemia in this patient is speculated to be related to β-thalassemia itself, β-thalassemia may directly lead to sustained immune stimulation (26, 27). The research focused on AIHA in patients with β-thalassemia is limited. β-thalassemia is caused by the absent (BETA^{0}) or insufficient (BETA^{+}) production of the β chain of the HGB. The imbalance of HGB chain synthesis in erythrocytes results in an excess of released α-globulin chains, which precipitate in precursors of erythrocytes and lead to structural changes in the cell membrane (28). The presence of these abnormal erythrocytes results in the continued activation of monocytes responsible for immune clearance, alterations of T and B lymphocytes, etc., that possibly be involved in the pathogenesis of AIHA (27, 29). Alloimmunization in patients with β-thalassemia major is usually associated with multiple

blood transfusion (27, 28). AIHA in the patient reported here was not transfusion dependent. The pathogenesis of MCD is also involved in the disorder of the immune system. The underlying mechanisms linking the AIHA and β-thalassemia minor in the current case requires further investigation. A study reported that seven patients with β-thalassemia major and AIHA received corticosteroid treatment and blood transfusion, in whom six patients responded well to the management, and the improved HGB remained stable for more than 6 months of following-up (30). The adult female β-thalassemia minor complicated with AIHA reported in this study did not respond well to the glucocorticoids and other immunosuppressant agents while treating the MCD (**Figure 4**). However, the use of RTX achieved pronounced efficacy on anemia and greatly improved the quality of life of the patient. The specific mechanism of action needs to be further studied.

In this study, an adult patient with refractory MCD with β-thalassemia minor complicated AIHA was treated with RTX and reached complete remission in both nephrotic syndrome and anemia. It could maintain the patient in a relatively stable remission state after the gradual withdrawal of non-specific immunosuppressants and glucocorticoids. There were no adverse effects reported or observed regarding the use of RTX during the observational periods. However, there are some limitations to this study. There is only one patient reported, and more similar cases need to be collected to verify the efficacy of RTX in such patients. Secondly, the follow-up after management with RTX is not too long, more observational period is required. Meantime, The refractory MCD and anemia caused by the β-thalassemia minor complicated AIHA reached complete remission after using RTX, while the anemia did not respond to the previous treatment with glucocorticoids and immunosuppressants management, what is the potential mechanism of RTX on them? The role of $CD20^+$ B lymphocytes in their pathogenesis needs to be further investigated.

In conclusion, the prevalence of refractory MCD with β-thalassemia minor complicated with autoimmune hemolysis seems to be lower than in the general population. We report a case of relatively successful treatment of this type of disease using $CD20^+$ B lymphocyte depletion biologic agent RTX, which may potentially provide a new choice for future clinical treatment strategy and mechanism exploration.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: The National Omics Data Encyclopedia (NODE), accession number: OEP003683.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region. Written informed consent to participate in this study was provided by the participant.

Author contributions

JZ, HJ, ZZ, CZ, XS, and CL made clinical data collection and actively involved in the clinical care of the patient. HJ and XT made substantial contributions to the research idea and study design. HJ and CZ evaluated the renal pathology of the patients. All authors contributed to important intellectual content during manuscript drafting and revision and accepted accountability for the overall work by ensuring that questions about the accuracy or integrity of any portion of the work are appropriately investigated and resolved and contributed to the article and approved the submitted version.

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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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Case report: A rare case of death due to end-stage renal disease caused by *Tripterygium wilfordii*-induced myelosuppression

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Tripterygium wilfordii—a traditional Chinese herbal medicine—is used to treat several diseases, including chronic kidney disease, rheumatic autoimmune disorder, and skin disorders. With the development of modern pharmacology, scientists have gradually realized that *T. wilfordii* has side effects on several organs and systems of the human body, including the liver, kidney, reproductive system, hematopoietic system, and immune system. Our understanding of its toxicity remains unclear. The incidence of problems in the hematopoietic system is not low but few related studies have been conducted. The serious consequences need to be of concern to clinicians and scientists. To ensure the safety of patients, it is important to elucidate the mechanism underlying the damage to the hematopoietic system caused by *T. wilfordii* and strategies to reduce its toxicity. Routine blood and biochemical tests should be conducted when administering *T. wilfordii*, and in case of any abnormality, the medication should be terminated in time along with a comprehensive symptomatic treatment. Herein, we report the case of a 50-year-old Chinese female with end-stage renal disease (ESRD) who developed severe bone marrow suppression after taking a short-term normal dose of a *T. wilfordii*-containing decoction. She died of sepsis and septic shock, although timely therapeutic measures (e.g., stimulating hematopoiesis, anti-infection treatment, and hemodialysis) were administered. To the best of our knowledge, this is the first report of death by *T. wilfordii*-induced myelosuppression from a short term, conventional dose in an adult female

with ESRD. Although the underlying mechanism remains unclear, this case contradicts the notion that side effects on the hematopoietic system are non-lethal.

KEYWORDS

traditional Chinese medicine, *Tripterygium wilfordii*, myelosuppression, end-stage renal disease, case report

Introduction

A 50-year-old female patient with end-stage renal disease (ESRD) who was not on renal replacement therapy took a *Tripterygium wilfordii*-containing decoction for 11 days, following which she developed obvious fatigue and scattered multiple subcutaneous ecchymoses on her lower limbs. The results of laboratory tests revealed abnormal coagulation function and peripheral hypocytosis mainly indicated by deceased leukocytes and platelets. Repeated bone marrow puncture results suggested acute suppression caused by medicinal ingredients. Later, the patient suffered a serious pulmonary infection. During her hospitalization, timely therapeutic measures were undertaken, including stopping the decoction usage, preventing bleeding, stimulating hematopoiesis, blood transfusion, anti-infection treatment, and hemodialysis. However, there was no change in the patient's condition owing to persistent bone marrow suppression. Finally, she died of sepsis and septic shock after 2 months due to a serious infection.

To the best of our knowledge, this is the first report of death in an adult female patient with ESRD who developed severe bone marrow suppression after taking a short-term normal dose of *T. wilfordii*-containing decoction. Although the underlying mechanism remains unclear, it contradicts the notion that side effects on the hematopoietic system are non-lethal. The safety of administering *T. wilfordii* to patients with ESRD needs further evaluation, and a more detailed study on the mechanism of its toxic effects is essential.

Case presentation

First hospitalization

On February 17, 2022, a 50-year-old Chinese female patient was admitted to Zhejiang University of Traditional Chinese Medicine First Affiliated Hospital in China with stage 5 chronic kidney disease, hypertension, renal anemia, and hyperuricemia. She had suffered from chronic kidney disease for more than 10 years, which developed into stage 5 approximately 2 years previously. Her renal pathological diagnosis was unclear. The patient was admitted for backache, nausea, and vomiting, and underwent a battery of routine tests (**Table 1**). Her body mass index (BMI) was 22.9. Physical examination was negative. Other examinations suggested that immunoglobulin G4, tumor markers, light chain test results, and thyroid function were normal. The antinuclear antibody spectrum showed a titer of 1:80; anti-Sjogren's syndrome antigen A/Ro antibodies were positive, but the patient denied the relevant suspected clinical manifestations. Computed tomography (CT) of the chest showed normal images (**Figure 1A**). Emission computed tomography (ECT) of the kidneys revealed that the estimated renal plasma flow (left kidney: 13.08 ml/min; right kidney: 32.31 ml/min) and glomerular filtration (left kidney: 2.13 ml/min; right kidney: 2.42 ml/min) rates were low. We advised renal replacement therapy to the patient, but she refused it and asked for conservative treatment. We formulated the following treatment plan: compound α-ketoacid 3.78 g–3 times per day, roxadustat 120 mg–3 times per week, felodipine 5 mg–twice a day, calcium dobesilate 0.5 g–3 times per day, sodium bicarbonate 1 g–3 times per day, febuxostat 40 mg once daily, and beraprost sodium 40 μg–3 times per day. The patient was discharged, and her follow-up was scheduled as a nephrology outpatient.

Second hospitalization

On May 04, a test of the patient's urine confirmed persistent proteinuria, and the patient agreed to be prescribed *T. wilfordii*-containing decoction per day to preserve residual renal function, but she requested an active treatment plan, so the dosage of *T. wilfordii* was set as 12 g per day, which was the maximum dose within the safe range, for 14 days. The patient was required to decoct *T. wilfordii* for 2 h first. We advised the patient to consult a nephrologist if she experienced any discomfort, including fever, subcutaneous ecchymosis, nausea, and vomiting; if not, routine blood and biochemical tests should be conducted after 2 weeks. The patient gave informed consent. 11 days later, the patient showed obvious fatigue and subcutaneous ecchymoses for the first time and discontinued the Chinese medication. On May 17, she visited our hospital and underwent relevant examinations (**Table 1**). Her BMI did not change.

TABLE 1 Laboratory data.

Variable	First hospitalization	Second hospitalization	Before death	Reference range
	02.18.2022	05.17.2022	06.17.2021	
Blood				
White blood cell count (per mm^3)	3,600	2,600	110	3,500-9,500
Neutrophils (%)	66.0	77.7	21.3	40-75
Lymphocytes (%)	23.1	16.7	40.2	20-50
Neutrophils (per mm^3)	2,400	2,000	10	1,800-6,310
Lymphocytes (per mm^3)	800	400	10	1,100-3,210
Red blood cell count (per mm^3)	2,660,000	2,320,000	2,020,000	3,800,000-5,100,000
Hemoglobin (g/l)	58	67	58	130-175
Platelet count (per mm^3)	487,000	21,000	5	125,000-350,000
Uric acid (μmol/l)	670	275	21	155-357
Creatinine (μmol/l)	171	299	80	45-84
Urea nitrogen (mmol/l)	10.76	36.1	11.9	2.6-7.5
Estimated glomerular filtration rate	13.02	15.31	77.92	
Total protein (g/l)	74.1	65.0	57.4	65.0-85.0
Albumin protein (g/l)	41.0	33.8	29.5	40.0-55.0
Potassium (mmol/l)	4.14	5.34	4.63	3.50-5.30
Sodium (mmol/l)	138.7	137.0	136.5	137.0-147.0
Chlorine (mmol/l)	104.2	103.2	101.7	99.0-110.0
Calcium (mmol/l)	2.27	2.20	2.30	2.10-2.60
Phosphorus (mmol/l)	1.51	1.66	0.42	0.81-1.65
Prothrombin time (s)	11.90	11.00	14.70	9.80-14.00
Prothrombin-time international normalized ratio	1.00	0.92	1.25	0.80-1.20
Fibrinogen (g/l)	4.18	3.83	5.22	2.00-4.00
Activated partial-thromboplastin time (s)	27.00	27.80	40.90	25.50-36.00
$_D$-Dimer (mg/l)	1.09	1.52	8.29	0.00-0.55
C-reactive protein (mg/l)	<1.00	2.91	238.94	0.00-8.00
Erythrocyte sedimentation rate (mm/h)	–	24	–	0-20
Brain natriuretic peptide (ng/l)	80.7	–	1397.3	0.0-100.0
Cardiac troponin I (μg/l)	–	–	0.037	0.000-0.026
Procalcitonin (μg/l)	–	–	2.360	0.000-0.046
Parathormone (pmol/l)	10.88	19.1	–	1.59-6.89
Arterial blood gas measurements				
pH	7.392	7.401	7.370	7.350-7.450
Partial pressure of carbon dioxide (mmHg)	36.2	35.3	43.0	35.0-48.0
Partial pressure of oxygen (mmHg)	115.0	108.0	121.0	80.0-100.0
Standard bicarbonate (mmol/l)	22.3	22.3	24.90	22.0-28.0
Actual bicarbonate (mmol/l)	21.6	21.5	24.80	22.0-28.0
Standard base excess (mmol/l)	−2.6	−2.6	−0.40	−3.00-3.00
Actual base excess (mmol/l)	−2.5	−2.5	−0.30	−3.00-3.00
Lactic acid (mmol/l)	0.70	0.80	0.80	0.5-2.2
Urine				
Color	Yellow	Yellow	–	
Clarity	Clear	Clear	–	
Specific gravity	1.008	1.009	–	1.003-1.030
pH	6.0	7.0	–	4.5-8.0
Protein	2 +	2 +	–	
α1-Microglobulin (mg/l)	83.73	96.51	–	0.00-12.50
β2-Microglobulin (μg/l)	21.04	64.15	–	0.0-300.0

(Continued)

TABLE 1 (Continued)

Variable	First hospitalization	Second hospitalization	Before death	Reference range
	02.18.2022	05.17.2022	06.17.2021	
Microalbumin (mg/l)	995.9	669.7	–	0.0-30.0
Microalbumin/creatinine (mg/mgCr)	2.029	2.158	–	0.000-0.030
White blood cells (/μl)	6.0	5.6	–	0.0-9.0
Red blood cells (/μl)	22.2	22.2	–	0.0-13.0

Jaffe's method was used to measure serum creatinine at our hospital. Before May 19, 2022, calcium dobesilate, which influences the detection of serum creatinine, was used to improve the patient's microcirculation.

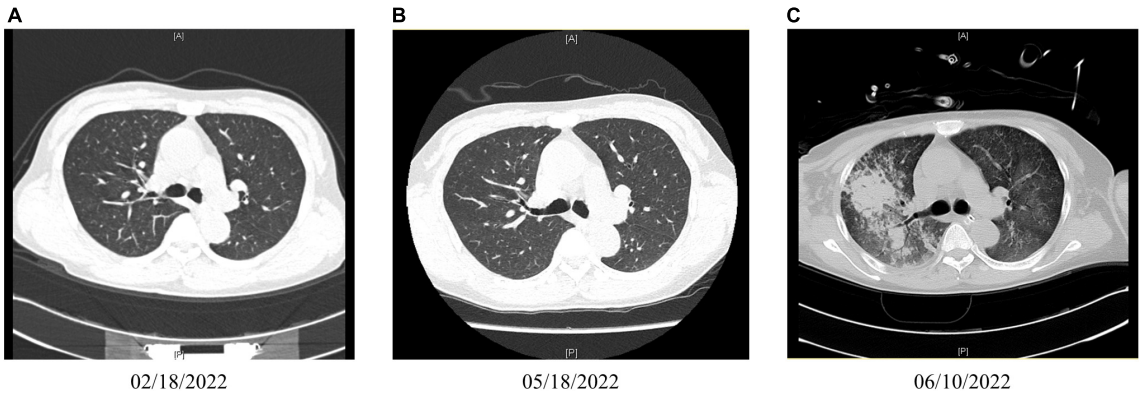


FIGURE 1
Chest imaging. **(A)** Normal computed tomography (CT) image taken on February 18, 2022. **(B)** Normal CT image taken on May 18, 2022. **(C)** The CT image taken on June 10, 2022 shows scattered large high-density shadows in both lungs.

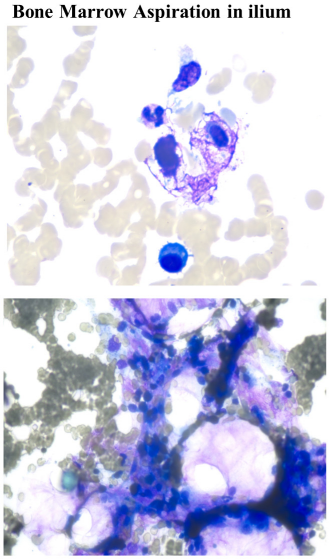
Physical examination was negative except for multiple scattered subcutaneous ecchymoses on her lower limbs. ECT of the patient's kidneys revealed a lower glomerular filtration rate (left kidney: 1.16 ml/min; right kidney: 2.52 ml/min) than before and estimated renal plasma flow was not detected. CT images of the chest were normal (Figure 1B). We admitted the patient to the intensive care unit. The patient showed obvious bone marrow suppression indicated by the deceased leukocytes and platelets, accompanied by abnormal coagulation function. However, she denied any previous hematopoietic system-related diseases. We prescribed dexamethasone, avatrombopag, recombinant human granulocyte colony-stimulating factor, recombinant human erythropoietin, and recombinant human thrombopoietin to stimulate hematopoiesis; carbazochrome sodium sulfonate to prevent bleeding; intravenous immunoglobulin to gain passive immunity; and repeated blood transfusion of red blood cells, albumin, human fibrinogen, platelets, and plasma. The patient consented to hemodialysis through a deep vein catheter. To clarify the cause of this condition, the hematology department was called upon for multidisciplinary combination therapy, and repeated bone marrow aspiration and biopsy were suggested (Figures 2A–C). The results showed that the patient's hematopoietic functions were seriously inhibited. A Coombs test excluded autoimmune hemolytic anemia. Considering her history, we diagnosed acute bone marrow hematopoietic stagnation caused by drugs.

The therapeutic schedule of this patient remained unaltered before and after the appearance of abnormal hematopoietic function, except for the addition of *T. wilfordii* to the patient's decoction. To the best of our knowledge, serious side effects related to the hematopoietic system have never been reported for the other herbal compounds in the decoction, based on "Buyang Huanwu Decoction" (1, 2), which was administered to the patient previously without any side effects on the hematopoietic system, for approximately 2 years. The composition formula is displayed in the Supplementary Table.

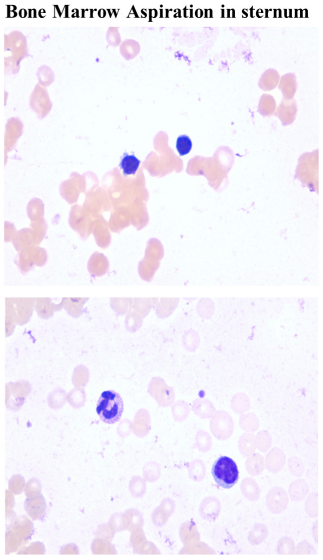
Combining with the results of blood routine tests before administering T. wilfordii, we believe that T. wilfordii caused bone marrow suppression (Figures 3A–C). Unfortunately, bone marrow suppression persisted throughout her second hospitalization. On May 31, the patient presented symptoms of dyspnea, cough, expectoration, and oxygen desaturation. CT images of the chest showed scattered large high-density shadows in both lungs, which suggested lung infection (Figure 1C). The results of sputum and blood culture suggested multidrug-resistant Enterobacter cloacae and carbapenem-resistant Acinetobacter Baumannii infection. Therefore, we administered several antibiotics including meropenem,

A

Bone Marrow Aspiration in ilium



Bone Marrow Aspiration in sternum



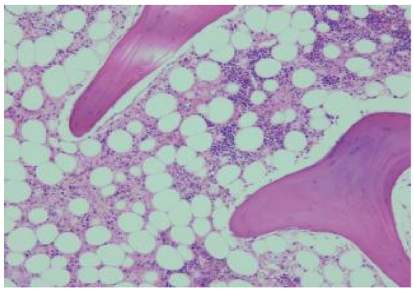
B

Cell Type	%	Reference range
Neutrophilic myelocyte	0.5	2.0-8.0
Neutrophilic granulocyte band form	13.5	9.5-28.5
Neutrophilic granulocyte segmented form	49.0	6.5-34.5
Polychromatophilic erythroblast	0.5	12.0-20.0
Orthochromatic erythroblast	5.0	6.0-20.0
Granulocyte/ Erythrocytoblast	11.5	2.0-4.0
Mature lymphocyte	27.5	5.0-20.0
Mature monocyte	1.5	0.0-5.0
mature plasma cell	2.0	-
histocyte	0.5	-

Cell Type	%	Reference range
Neutrophilic granulocyte band form	3.5	9.5-28.5
Neutrophilic granulocyte segmented form	31.0	6.5-34.5
Orthochromatic erythroblast	5.0	6.0-20.0
Granulocyte/ Erythrocytoblast	6.9	2.0-4.0
Mature lymphocyte	60.0	5.0-20.0
Mature monocyte	0.5	0.0-5.0

C

Bone Marrow Biopsy



Immunohistochemistry
CD34 (neg), CD117 (dim), MPO (mod), CD15 (mod), CD235a (mod), E-cad (mod), CD61 (dim), CD20 (dim), CD3 (dim), CD138 (dim), Kappa (dim), Lambda (dim) , Reticular fiber (neg), Perls (neg)

FIGURE 2
Bone marrow aspiration, biopsy, and immunohistochemistry. Bone marrow aspiration was performed using Wright's staining technique. Bone marrow biopsy and immunohistochemistry were performed using staining techniques involving hematoxylin, Giemsa, acid fuchsin, reticular fiber, and Prussian blue stains. **(A)** Bone marrow aspiration in ilium performed on May 20, 2022. The results reveal low proliferation of nucleated cells without abnormality in morphology. **(B)** Bone marrow aspiration in sternum performed on May 24, 2022. The results reveal low proliferation of nucleated cells without abnormality in morphology. **(C)** Bone marrow biopsy and immunohistochemistry performed on May 20, 2022. Hematopoietic elements are substantially reduced (30%), and bone marrow space is replaced with adipose tissue (70%). Granulocyte and erythrocyte development are normal.

polymyxin, tigecycline, cefoperazone sodium, and sulbactam sodium successively to treat the infection.

Results

After more than 1 month of treatment, on June 18, the patient died of sepsis and septic shock.

Discussion

Efficacy of *Tripterygium wilfordii*

Tripterygium wilfordii Hook, belonging to Tripterygium of Celastraceae, has been used as a traditional Chinese medicine for hundreds of years. It is widely used to treat various diseases and shows remarkable curative effects. *T. wilfordii* is an antirheumatic Chinese medicinal herb. The earliest record that systematically summarized its efficacy in China is in "Ben Cao Gang Mu Shi Yi," a book dating back nearly 300 years. It is used to treat various diseases including chronic renal disease, rheumatic immune disease, and skin disease (3). A meta-analysis of the treatment of chronic renal disease with *T. wilfordii* polycoride has shown that *T. wilfordii* can alleviate proteinuria and delay the progression of chronic renal disease (4).

Modern pharmacology suggests that *T. wilfordii* exerts anti-tumor, anti-inflammatory, and immunosuppressive effects (5, 6), and its main active ingredients are triptolide, celastrol, and total alkaloids of T. hypoglaucum (7). Its excellent curative effect is accompanied by some side effects; thus, scientists have conducted several studies to identify its toxic components and side effects and develop strategies to reduce them (8, 9). The toxic components and active components of T. wilfordii are largely overlapping. For example, triptolide, a diterpenoid epoxide in T. wilfordii, is a medicinal and noxious compound (7, 10).

Methods of *Tripterygium wilfordii* drug delivery

At present, *T. wilfordii* is used clinically in two ways in China. One way is to use it in decoctions. Some studies have shown that combining it with other traditional Chinese medicines, such as licorice, silymarin, and ginseng, can help reduce the toxicity of *T. wilfordii* (11–13). The reference dose is different among Chinese pharmacopoeias and herbal guidelines. For example, the Traditional Chinese Pharmacology stipulated a dosage of 1–3 g of *T. wilfordii* per prescription in the formula and decoction time of 45–60 min before adding other herbs (14). In contrast, the Chinese Materia Medica recommended a dosage of 10–12 g of *T. wilfordii* per prescription in the formula and decoction time of 1–2 h (15). Our hospital suggests that the initial dosage of *T. wilfordii* should be different according to the patient's weight. For adult patients weighing less than 60 kg, the dosage is 3 g per day; for those weighing more than or equal to 60 kg, it is 5 g per day. If there is no adverse reaction, the dose is increased to 12 g per day at most. The herb should be decocted for 2 h first. Considering that not all toxic substances have therapeutic effects, another method is to extract the effective components of *T. wilfordii* and convert them into a patented Chinese medicine to reduce toxicity. Among several preparations, *T. wilfordii* polycoride is the most convenient and widely used preparation, containing diterpene lactones, alkaloids, and triterpenoids (16). According to the Chinese Pharmacopoeia and National Standards published in 2010, the *T. wilfordii* lactone content should be not less than 0.1 mg/g/tablet; the recommended dose is 1.0–1.5 mg/kg/day, administered three times a day after meals (17).

In recent years, new methods of drug delivery have been proposed. Wang et al. attempted a transdermal microemulsion drug delivery system for *T. wilfordii* Hook f. to ameliorate its toxic effects on the male reproductive system (18). Xue et al. reported the protective effects of *Tripterygium* glycoside-loaded solid lipid nanoparticles against toxicity to the male reproductive system (19). However, these drug delivery methods neither demonstrate protection of the kidney or hematopoietic system nor are widely used for now.

Tripterygium wilfordii toxicity

Tripterygium wilfordii affects various systems and organs, causing reproductive toxicity (20), liver damage (21), and kidney damage (22). Relevant studies have focused on these aspects (23–25). The toxicity of *T. wilfordii* is generally considered to be related to its dose and duration, and most of the side effects are reversible (26). However, *T. wilfordii* sometimes causes damage to the hematopoietic system, which usually manifests as leukopenia and aplastic anemia (27). The incidence of this side effect is lower than that of liver injury, but not uncommon, and its mechanism is unclear (4, 27, 28). According to Kusy et al., celastrol, an important component of *T. wilfordii*, specifically impairs the development of B cells and erythrocytes in the peripheral blood, bone marrow, spleen, and peritoneal cavity, but in mature lineages, the adverse effects are transient, as recovery is complete 4 weeks after the removal of the drug (29). Pyatt et al. suggested that *T. wilfordii* directly blocks the ability of very early multilineage as well as lineage-specific committed hematopoietic progenitor cells to form colonies in a dose-dependent way, which might be related to nuclear factor-kappa B signaling (30). These studies cannot fully explain the conditions found in this case.

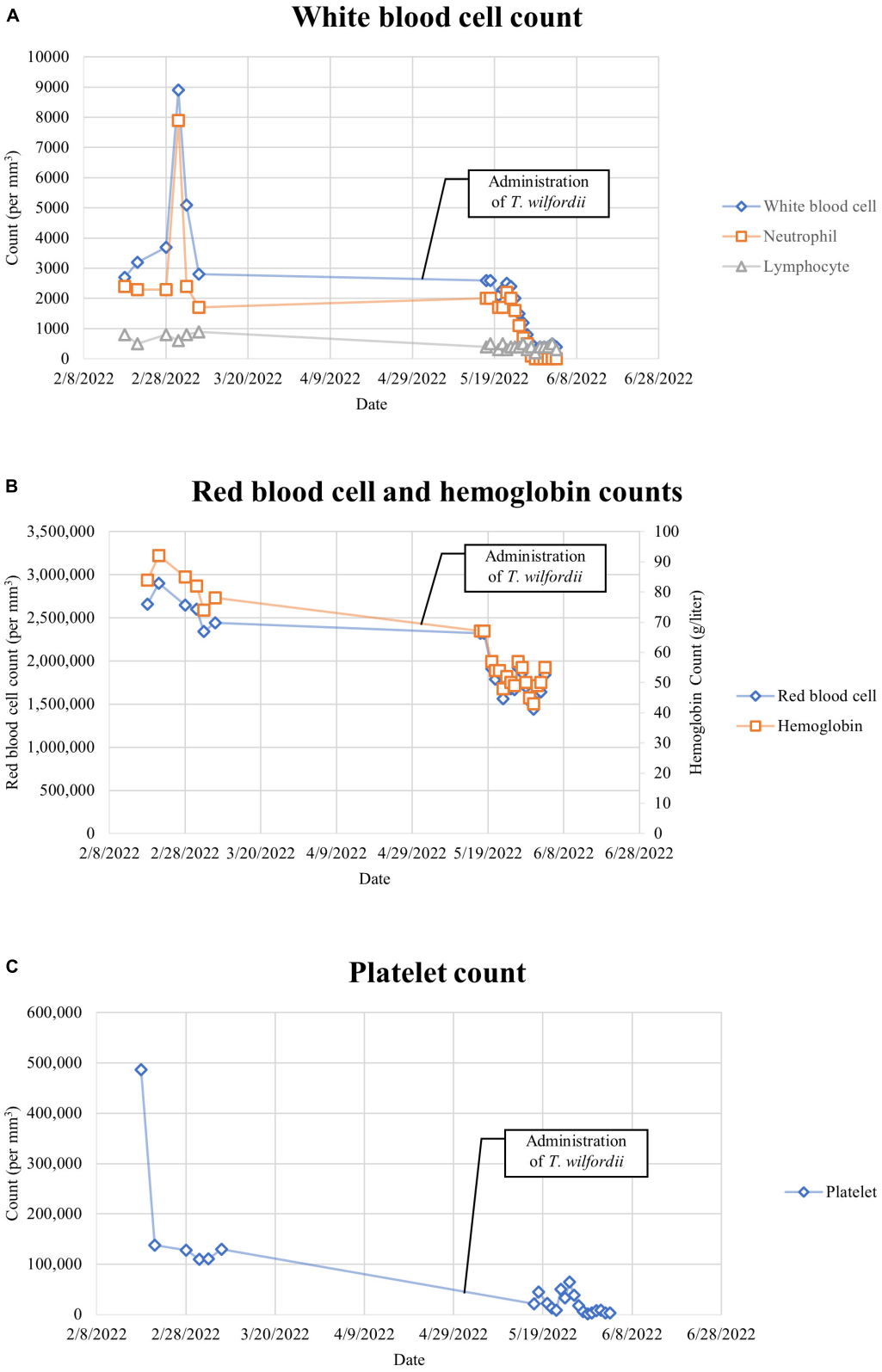


FIGURE 3
(A) White blood cell count. The normal reference ranges of the above data are listed in **Table 1**. **(B)** Red blood cell and hemoglobin counts. The normal reference ranges of the above data are listed in **Table 1**. **(C)** Platelet count. The normal reference ranges of the above data are listed in **Table 1**.

Wu et al. (31), Feng et al. (32), and Liu et al. (33) reported several severe cases of bone marrow suppression caused by excessive doses or long-term use of *T. wilfordii*. The medicine was terminated in these cases and blood transfusion was performed to stimulate the hematopoietic system. The patients were eventually rescued and bone marrow suppression was eliminated.

Case characteristics

To the best of our knowledge, this is the first report of death in an adult female patient with ESRD caused by severe bone marrow suppression after taking a short-term normal dose of a *T. wilfordii*-containing decoction. This finding contradicts the prevailing belief that side effects on the hematopoietic system are non-lethal. The patient had no previous hematopoietic system-related diseases, dosage of *T. wilfordii* decoction complied with the specifications, consumption duration was short, and medication was stopped immediately after symptoms were detected. Therefore, the cause of severe bone marrow suppression was unclear. Subsequent treatment continued for nearly 2 months; however, the patient did not recover and finally died of serious infection. It is unknown whether ESRD was involved in the occurrence of bone marrow suppression. From this case study, it is reasonable to conclude that *T. wilfordii* side effects are probably not only limited to toxic accumulation, but also related to the immune system, thereby triggering hematopoietic cell destruction. Moreover, we cannot exclude the possibility of rare idiosyncratic drug reactions (34). However, owing to the lack of relevant basic research, further studies are required to confirm these conjectures.

Limitations

This case report has some limitations. First, owing to the complex ingredients of *T. wilfordii* decoction, we could not detect the blood concentration of *T. wilfordii*. Thus, it is difficult to directly confirm whether bone marrow suppression was caused by the toxic accumulation of *T. wilfordii*. Second, according to the recommendations of the Chinese Materia Medica and Traditional Chinese Pharmacology, *T. wilfordii* is toxic and needs to be decocted for a long time to reduce toxicity before adding other herbs (14, 15). Although the patient was instructed to decoct *T. wilfordii* for 2 h, we could not determine whether this was strictly performed. Finally, the reference dosage of *T. wilfordii* varies greatly among guidelines. We may not propose the most effective and safe reference dosage for patients with chronic kidney disease due to the lack of relevant study.

Future research directions

Proposals for novel methods of drug delivery to alleviate *T. wilfordii* toxicity are essential. At present, the content of TWHF in *T. wilfordii* polyglycoside tablets varies among manufacturers (35). It is necessary to quantify blood drug concentration in clinical settings. Pharmacokinetic studies and safety evaluation of *T. wilfordii* should be continued. Genetic testing may verify whether the severe side effects of *T. wilfordii* are related to heredity. Detailed medication guidelines should be prepared for patients with liver or kidney damage, pregnant women, and the elderly population. The mechanisms underlying the toxic effects should be studied in detail to avoid bone marrow suppression, and a systematic treatment plan to prevent side effects should be prepared.

Conclusion

Although *T. wilfordii* has been used for hundreds of years, our understanding of its toxic effects remains incomplete, and the mechanism remains unclear. In addition to reproductive toxicity and liver and kidney injuries, hematopoietic system problems are possible. These serious consequences deserve clinicians' attention. When using *T. wilfordii*, the initial dose should be small and routine blood and biochemical tests should be conducted regularly. In case of abnormalities, the medicine should be stopped in time and symptomatic treatments should be provided. The safety of *T. wilfordii* in patients with ESRD requires detailed evaluation. Elucidating the mechanism of *T. wilfordii*-induced hematopoietic system damage and seeking new methods to reduce its toxicity are necessary for clinical applications.

Data availability statement

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

Ethics statement

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

Author contributions

WZ and XL researched data and wrote the manuscript. CX, LH, HM, XW, and PZ reviewed the manuscript.

All authors contributed to the article and approved the submitted version.

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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

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Case report: Acute oxalate nephropathy due to traditional medicinal herbs

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Acute oxalate nephropathy (AON), defined as the association between acute kidney injury (AKI) and the deposition of oxalate crystals in the renal parenchyma, is a rare complication of hyperoxaluria. We report a rare case of AON in an adult due to medicinal herbs intake leading to crystal-induced AKI. We recommend that a thorough medication history including the use of medicinal herbs, should be obtained for all patients with a rapid loss of kidney function, especially in the absence of known risk factors for AKI. The use of medicinal herbs with unknown oxalate contents would increase the risk of AON and should be avoided.

KEYWORDS

acute kidney injury, acute oxalate nephropathy, medicinal herbs, hyperoxaluria, renal biopsy

Introduction

Oxalate is originated endogenously from the metabolism of amino acids or exogenously from the intake of oxalate-rich foods (1). The kidney is the sole organ responsible for oxalate excretion (2). Excessive oxalate in the kidney causes the formation of insoluble calcium oxalate crystals (3). This, in turn, leads to a spectrum of kidney disorders, including nephrolithiasis, nephrocalcinosis, and acute oxalate nephropathy (AON) (4). AON can be observed with primary hyperoxaluria (PH) (5) and secondary hyperoxaluria (SH) (6), with the first being inborn errors of metabolism and the second a result of enteric hyperoxaluria or excessive oxalate intake.

Here, we describe a case of acute kidney injury (AKI) after excessive ingestion of Chinese medicinal herbs with previously normal renal function, with tubular deposition of oxalate crystals evident on renal biopsy.

Case

A 25-year-old male patient presented to the emergency room with recurrent episodes of lumbar pain, nausea, and vomiting in the preceding days. The patient

was healthy and had no previous medical problems. A family history of urolithiasis was not noted. Laboratory workup revealed non-oliguric AKI with a serum creatinine of 237 μmol/L, elevated from a stable baseline of 84 μmol/L. Post-renal causes were excluded because the renal ultrasound did not show any signs of obstructive nephropathy or intra-renal or ureteral concrements. The patient was transferred to the nephrology department for further evaluation.

Except for the bilateral costovertebral angle and lower abdominal tenderness, the rest of the physical examination findings were unremarkable. Renal function was severely deteriorated with serum creatinine levels of 724 μmol/L and urea nitrogen level of 21.75 mmol/L. Electrolytes showed potassium of 4.86 mmol/L and sodium of 136 mmol/L. Laboratory findings demonstrated that parathyroid functions were within the normal range: calcium 2.41 mmol/L, phosphorus 1.43 mmol/L, and intact parathyroid hormone (PTH) 38.45 pg/ml (15–65 pg/ml). The liver function test results were unremarkable. Serological test revealed normal levels of immunoglobulin, complements and antinuclear antibodies. ANCA-antibodies and anti-GBM-antibodies were negative. His 24-h urine protein collection was normal (0.08 g/24 h), but the urine albumin-to-creatinine ratio was slightly elevated at 8.16 mg/mmol. Abdominal computed tomography (CT) were normal.

The calculated fractional excretion of sodium (FeNa) was 1.6% and renal function did not improve upon intravenous volume challenge. As such, pre-renal AKI is unlikely. Since the etiology of AKI remains unknown, a renal biopsy was performed, which showed features of severe acute tubular necrosis without infiltration of inflammatory cells. Abundant tubular calcium oxalate deposits were detected within the tubular lumen (**Figure 1**). Additional laboratory tests revealed elevated urinary oxalate excretion (1.11 mmol/24 h). Mutations in AGXT, GRHPR, and HOGA1 in PH were not detected (7) (**Supplementary Appendix 1**).

Upon further questioning, the patient reported an ingestion of approximately 30 g (dry weight) of a mixture of several herbs (*Panax notoginseng, Clematis chinensis Osbeck, Szechwan Lovage Rhizome, borneol, safflower,* and *Eupolyphaga sinensis*) per day in the last 4 weeks before admission for ankle sprain. This traditional remedy is in powder form and mixed with water. He said that the ingestion of such remedies was a customary practice in his hometown. Consumption of vitamin C or ethylene glycol was ruled out.

Elevated urine oxalate levels and renal biopsy led to the diagnosis of oxalate nephropathy, which is the most likely cause of AKI. Given the lack of other explanations, hyperoxaluria was believed to be due to excessive intake of oxalate-rich herbs.

Due to uremic symptoms, emergent hemodialysis *via* a temporary catheter was started before renal biopsy. Totally, three standard hemodialysis were conducted on an Artis hemodialysis machine (Gambro Lundia AB, Lund, Sweden) with a low-flux polysulphon dialyzer F6 (Fresenius Medical Care, Bad Hamburg, Germany). Serum creatinine peaked at 211 μmol/L before plateauing with cessation of dialysis. Once the diagnosis is established, the patient was advised to avoid a high oxalate diet, drink plenty of water (>3 L/1.73 m^2) and consume calcium acetate (1,334 mg orally with each meal), and potassium citrate (2 g/day, orally). By the day of discharge, renal function had partially recovered, and creatinine levels had decreased to 137 μmol/L. His creatinine level improved and plateaued at 103 μmol/L at 12 months follow-up. **Table 1** describes the renal function tests of the patient.

Discussion

Acute oxalate nephropathy, defined as the association between AKI and the deposition of oxalate crystals in the

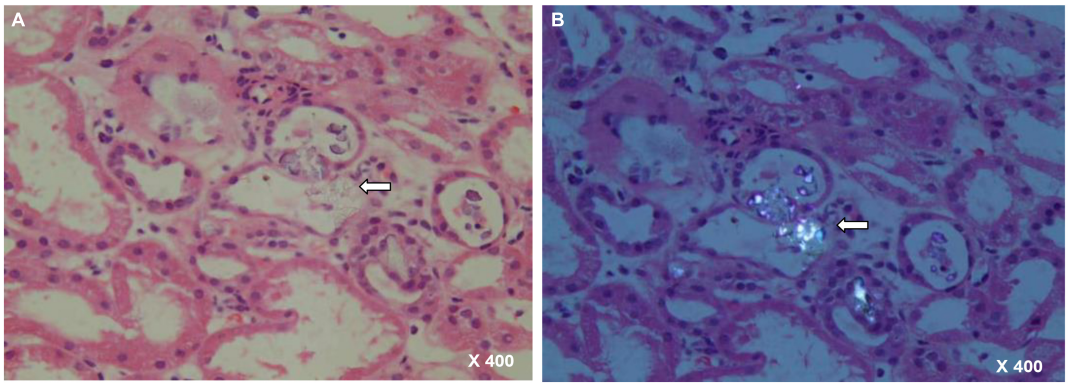

FIGURE 1
Renal biopsy specimen with arrow showing a couple of calcium oxalate deposits within renal tubules. **(A)** HE staining, 400× magnification. **(B)** Polarized light, 400× magnification.

TABLE 1 Trend in renal function panel and clinical therapy review.

Timeline line	Day 0 (admission)	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7	Day 10	Day 13 (discharge)	1 months after discharge	3 months after discharge	6 months after discharge	12 months after discharge
Serum creatinine (μmol/L)	724	925			508		211	171	137	101	103	100	103
Blood urea nitrogen (mmol/L)	21.75	21.8			16.54		6.5	6.35	6.8	3.80	4.37	5.72	5.41
eGFR (ml/min/1.73 m^2) (**CKD-EPI equation**)		8.2							60.2	88.3	86.8	89.3	85
Renal biopsy				√									
Oxalate binder therapy					CA #	CA #	CA #	CA #	CA #	CA #			
					PC*	PC*	PC*	PC*	PC*	PC*			
Intermittent hemodialysis			√			√	√						

CA #, calcium acetate (1334 mg orally with each meal); PC*, potassium citrate (2 g/day). Intermittent hemodialysis was conducted using a Artis hemodialysis machine (Gambro Lundia AB, Lund, Sweden) with a low-flux polysulphon dialyzer F6 (Fresenius Medical Care, Bad Hamburg, Germany).

renal parenchyma, is a rare complication of hyperoxaluria. In the present case, renal biopsy under polarized light revealed massive oxalate crystals in the tubular lumen. This highlights the importance of histopathological confirmations of AON.

Acute oxalate nephropathy can occur due to PH or SH (5, 6). PHs comprise a group of three distinct genetic disorders of glyoxylate metabolism, characterized by endogenous oxalate overproduction (7). Patients with PH typically develop recurrent renal lithiasis and progressive nephrocalcinosis (8). Our patient had no personal history of lithiasis and the genetic testing results were normal. Thus, the clinical picture in our patient was not consistent with a diagnosis of PH.

Secondary hyperoxaluria is more common. The leading cause of SH is enteric hyperoxaluria (9), which is usually a consequence of fat malabsorption (10). In enteric hyperoxaluria, fat malabsorption leads to increased binding of calcium to free fatty acids, resulting in more soluble oxalates in the intestinal lumen, which are subsequently absorbed (11). Enteric hyperoxaluria is often present in patients with inflammatory bowel disease, celiac disease, short bowel syndrome, chronic pancreatitis, or bariatric surgery (12–16). However, our patient showed no clinical symptoms of fat malabsorption.

Increased intake of dietary oxalate or oxalate precursor (such as ethylene glycol or vitamin C) can also contribute to AON (17–20). Prior reports have described patients with oxalate nephropathy due to hyperoxaluria after ingesting oxalate-rich food (17, 18). Dietary sources rich in oxalate include nuts, plums, chocolate, beetroot, strawberries, and spinach (21). Our patient occasionally consumed these foods. In addition, he denied the use of ethylene glycol products or consumption of vitamin C. Therefore, it is unlikely that the dietary oxalate or oxalate precursor was the culprit.

Traditional herbal medicines are naturally occurring, plant or animal-derived substances that are not processed to treat diseases according to local practices. In a study by Huang et al. (22), the total oxalate content of 22 herbs ranged from 165 to 3,204 mg/100 g, which was much higher than that of daily foods such as various flours and nuts. Different medicinal herbs, even those from the same family, contain significantly different amounts of oxalate (22). Oxalate nephropathy has been reported following the consumption of medicinal herbs, such as rhubarb and star fruit (23, 24). In the present case, the absence of evidence for any other cause of AON incriminates the herbal mixture as the culprit. There are no previous case reports in the literature describing oxalate nephropathy in association with any of the involved herbs in our patient. The concentration of oxalate in the same herb may be quite different in different place of origin. Different parts of the same herb, even those from the same place of origin, contain significantly different amounts of oxalate. Due to the lack of detailed information, the concentration of oxalate in each herb was not tested in our

study. Thus, it is not known which component of the mixture is responsible for AON. Even so, the findings from our case, at least to some extent, indicate that the use of medicinal herbs with unknown oxalate contents may increase the risk of AON.

We report a rare case of AON in an adult due to medicinal herbs intake leading to crystal-induced AKI. We recommend that a thorough medication history including the use of medicinal herbs, should be obtained for all patients with a rapid loss of kidney function, especially in the absence of known risk factors for AKI. The use of medicinal herbs with unknown oxalate contents would increase the risk of AON and should be avoided.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary material**.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. 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

ZZ and JL reviewed the medical literature and clinically managed the patients and manuscript. LW reviewed the relevant histopathology and prepared the figure and manuscript. All authors contributed to the conception, drafting, and final approval of the submitted work.

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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ADTKD-*UMOD* in a girl with a *de novo* mutation: A case report

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Autosomal dominant tubulointerstitial kidney disease due to *UMOD* mutations (ADTKD-*UMOD*) is a rare condition associated with high variability in the age of end-stage kidney disease (ESKD). An autosomal dominant inheritance is the general rule, but *de novo UMOD* mutations have been reported. It was reported that the median age of ESKD was 47 years (18–87 years) and men were at a much higher risk of progression to ESKD. Here, we reported a 13-year-old young girl with unexplained chronic kidney disease (CKD) (elevated serum creatine) and no positive family history. Non-specific clinical and histological manifestations and the absence of evidence for kidney disease of other etiology raised strong suspicion for ADTKD. Trio whole-exome sequencing confirmed that she carried a *de novo* heterozygous mutation c.280T > C (p.Cys94Arg) in the *UMOD* gene. The functional significance of the novel mutation was supported by a structural biology approach. With no targeted therapy, she was treated as CKD and followed up regularly. The case underscores the clinical importance of a gene-based unifying terminology help to identify under-recognized causes of CKD, and it demonstrates the value of whole-exome sequencing in unsolved CKD.

KEYWORDS

ADTKD, *UMOD*, *de novo* mutation, case report, genetic kidney disease

1 Introduction

ADTKD is a rare genetically heterogeneous disorder characterized by slowly progressive loss of kidney function, and bland urinary sediment with absent or trace proteinuria. A gene-based sub classification has been proposed by Kidney Disease: Improving Global Outcomes (KDIGO) (1). The most prominent features of Autosomal dominant tubulointerstitial kidney disease due to *UMOD* mutations (ADTKD-*UMOD*)

include early onset hyperuricemia (gout) and/or a family history of hyperuricemia (2, 3). Compared to ADTKD-*MUC1*, ADTKD-*UMOD* seems to be associated with an earlier age at disease presentation but a later age to end-stage kidney disease (ESKD) (4). The age for development of ESKD ranges from 18 to 87 years, and renal fibrosis is the common feature (2). Because those clinical manifestations are mostly non-specific, so the diagnosis of ADTKD in practice is difficult and currently relies on positive family history and genetic sequencing (1, 2).

2 Case report

A 13-year-old girl presented to our hospital with a 1-month history of abnormal renal function. She was a student of middle school and had no special medical, family, or psycho-social history. On a physical examination, she had a serum creatinine of 164 μmol/L (Schwartz Pediatric eGFR 40 ml/min), urea 15.1 mmol/L, and blood pressure 140/90 mmHg, without any discomfort. She had an elevated serum uric acid level of 438 μmol/L but hadn't experienced gout symptoms. Urine sediment analysis was normal, and 24 h urine protein was only 0.24 g/2,000 ml. She had some clinical features of tubular injury, such as low morning urine osmolality (312 mOsm/kg), high level of urinary α1 microglobulin (22.9 mg/L, range 0–12 mg/L), and compromised renal acid-base handling ability, including lower urine bicarbonate (2.7 mmol/L, normal range < 26.8 mmol/L), titratable acid (4.3 mmol/L, normal range > 10.5 mmol/L), and ammonium ion (0.2 mmol/L, normal range > 25.2 mmol/L). Her hemoglobin level was normal (120 g/L) but iPTH (556.7 μg/ml, normal range 15–65 μg/ml) was elevated. Detailed clinical information was listed in **Table 1**. She had normal sized kidney of 10.5 cm in length. However, magnetic resonance imaging (MRI) of the kidneys revealed some occasional cysts at the corticomedullary boundary (**Figure 1A**). Without any indications of a thick-walled bladder, ureteric dilatation, and hydronephrosis for urological anomalies, the family refused voiding cystourethrography (VCUG).

The immunoglobulin levels were normal and no autoantibodies were found. The patient's IgG4 was mildly elevated at 2.48 g/L (normal range < 2.01 g/L), and C3 was slightly decreased at 0.59 g/L (normal range 0.6–1.5 g/L). MRI showed no evidence of other organ involvement. The patient denied any recent infections, toxic drug exposure, or any family history of kidney disease. Secondary hypertension due to obstructive sleep apnea, primary aldosteronism, pheochromocytoma, hyperthyroidism, renovascular disease, renal artery stenosis, aortic coarctation, and inflammatory or systemic conditions were also ruled out.

With informed consent, a kidney biopsy was performed to further identify the etiology and the severity of the tubulointerstitial injury. No evidence of immune complex deposition or inflammation or cell proliferation. Light microscopy showed tubulointerstitial fibrosis, atrophy, cystic dilatation of tubules, and widely distributed global glomerulosclerosis (83%). Electron microscopy showed mitochondrial swelling, focal cristae damage, and vacuolation of tubular cells (**Figures 1B–D**). Glomerulonephritis, IgG4-related disease, and alport syndrome were ruled out (**Figure 1E**).

According to the above results, she was suspected of a possible diagnosis of ADTKD. However, abnormal UMOD accumulations, typically as polymorphic unstructured materials by PAS staining, were not noteworthy (**Figure 1F**). Thus the trio whole-exome sequencing was then performed. A *de novo* heterozygous mutation c.280T > C (p.Cys94Arg) in the *UMOD* gene was found, which was absent in her parents (**Figure 2A**). The mutation was predicted to be deleterious and has been reported in a clinical case associated with hyperuricemic nephropathy (5). A different amino acid substitution at the

TABLE 1 Clinical information and treatment of the patient.

Item	Value	Normal range
Hemoglobin	120 g/L	115–150 g/L
Albumin	38.5 g/L ↓	40–55 g/L
White blood cells	9*10^9/L	3.5–9.5*10^9/L
Serum creatinine	164 μmol/L ↑	44–133 μmol/L
Urea	15.1 mmol/L ↑	1.8–7.1 mmol/L
eGFR	40 ml/min ↓	
Uric acid	438 μmol/L ↑	90–360 μmol/L
Na^+	137.79 mmol/L	135–145 mmol/L
K^+	3.57 mmol/L	3.5–5.5 mmol/L
Urinary α1 microglobulin	22.9 mg/L ↑	0–12 mg/L
Urinary N-Acetyl-B-D-Glucosaminidase	6.5 U/L	0.3–12 U/L
Urine red blood cell	1.2/HP	0–7/HP
24 h urine protein	0.24 g/2,000 ml ↑	0–0.15 g/24 h
Urine pH	6.0	4.5–8.0
Urine bicarbonate	2.7 mmol/L	0–26.8 mmol/L
Titratable acid	4.3 mmol/L ↓	> 10.5 mmol/L
Ammonium ion	0.2 mmol/L ↓	> 25.2 mmol/L
Urine osmolality	312 mOsm/kg ↓	600–1,000 mOsm/kg
Treatment	**BP control:** Amlodipine 2.5 mg bid; Betaloc 47.5 mg qd	
	Hyperuricemia control: Febuxostat 20 mg qd; Sodium bicarbonate: 0.5 g tid	
	Prednisone 40 mg qd (Gradual tapering and discontinuation after 6 months)	

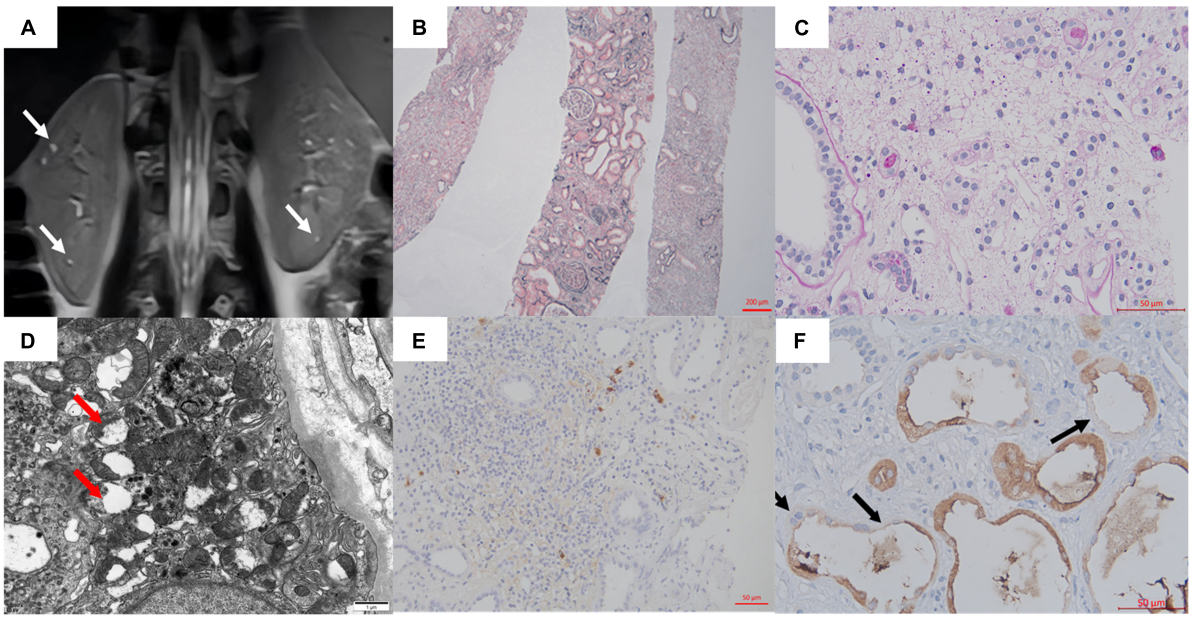

FIGURE 1
(A) MRI showed multiple microscopic cysts in the medulla of the patient's kidney. **(B,C)** Interstitial edema and tubular destruction (PAS 400×). **(D)** Transmission electron micrograph of tubular epithelial cytoplasm showed mitochondrial swelling, focal cristae damage, and vacuolation (arrows). **(E)** The IgG4 staining in the interstitium. **(F)** Uromodulin was expressed in the cytoplasm of most cells of the thick ascending limb of Henle. Some epithelial cells were negative or weakly/partial UMOD positive along the luminal side (arrows). No UMOD protein accumulation was observed (400×).

same site (p.Cys94Trp) has been reported in patient with ADTKD (2). According to the 2015 ACMG genetic variant classification criteria and guideline (6), it was defined as a likely pathogenic variant (PS2 + PM5 + PP3). For molecular function, the mutation was located in the EGF-2 domain (position 65–107), which was associated with calcium binding. To further predict the effect of the mutation on the tertiary structure of the protein, we created a 3D structural model of UMOD protein using Phyre2 (7) and analyzed the mutated protein using Missense3D (8), VarSite (9), and PyMOL (10). Results showed that the substitution disrupted the disulfide bond with its interacting residue Cys106 (Distance: 2.151 Å) on the chain, triggering a clash alert, with the predicted local clash score for the mutant and the wild type being 87.17 and 40.69, respectively. In addition, the mutant arginine was more hydrophilic, which might prefer protein surface to the interior and result in protein misfolding (**Figure 2B**).

We gave the patient supportive treatment (1, 11) of amlodipine, betaloc for blood pressure control, and febuxostat, sodium bicarbonate for hyperuricemia. Because initially we cannot rule out immune-related kidney injury with her abnormal levels of C3 and IgG4, prednisone with an initial dose of 40 mg per day was tentatively added. However, it showed no beneficial effect and was stopped 6 months later. The detailed regimen was listed in **Table 1**. The patient has been followed up over 2 years till date. Her serum creatinine gradually elevated to about 345 μmol/L (Schwartz Pediatric eGFR 16 ml/min), despite her well-controlled serum uric acid (< 320 μmol/L), urine protein (< 0.5 g/24 h), and blood pressure (around 120/80 mmHg).

3 Discussion

We presented the case of a 13-year-old girl with unexplained abnormal renal function with the main manifestation of renal tubular interstitial damage. Despite her reported negative family history, the patient was suspected of genetic kidney disorder after a careful workshop of both clinical and pathological investigations. Using the new clinical *UMOD*-scoring system proposed in 2020 (2), our patient had a score of 6 (over 5 was suggested as a possibility of ADTKD-*UMOD*). Therefore, trio WES was performed and a *de novo* mutation in the *UMOD* gene was identified. According to the current KDIGO diagnostic criteria, positive family history was a prerequisite in establishing the diagnosis of ADTKD (1). But a negative family history may not exclude the diagnosis. There have been a few case reports with *de novo* mutations in *UMOD* (4). We highlighted that, for some young patients (positive or negative family history) with unexplained decreased kidney function, the possibility of hereditary kidney disease needs to be considered and genetic sequencing needs to be actively performed.

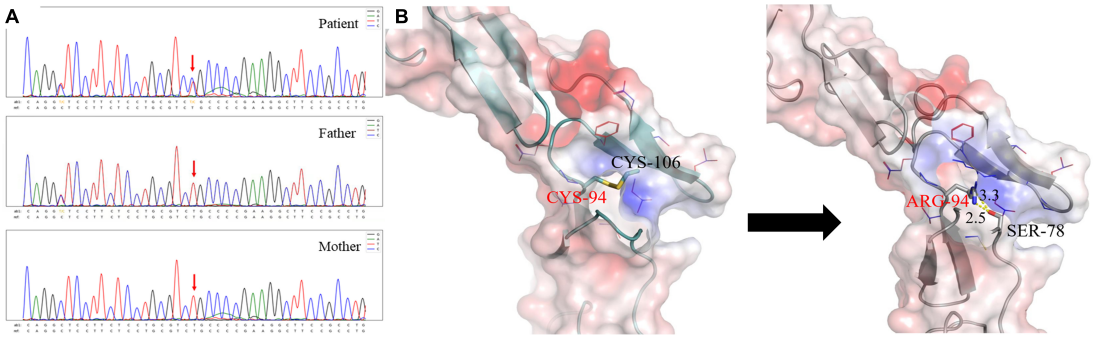

FIGURE 2
(A) The patient carried a heterozygous mutation in the UMOD gene c.280T > C (p.C94R), and neither of her parents carried this mutation. **(B)** Different interaction patterns in wild type and p.C94R mutant. The left one is for the wild-type structure and the right one is for the p.C94R mutant. The electrostatic surface is colored according to a scale from red (negative, min = −5.0 kT/e) to blue (positively, max = 5.0 kT/e). The backbone structure is shown in cartoon representation, Cys94, Cys106, and Ser78 as sticks with the rest of the side chains as lines. The distance between the hydrogen donor and the hydrogen acceptor is marked in the unit of Angstrom (Å).

In addition to genetic diagnosis, in this case, MRI of the kidneys revealed some occasional cysts at the corticomedullary boundary, which was characteristic of ADTKD. And the effectiveness of MRI for the identification of ADTKD cysts has been confirmed in previous reports (12). Besides, immunohistochemistry may provide clues such as abnormalities in uromodulin staining, i.e., coarsely granular cytoplasmic staining or perinuclear positivity in flattened tubular epithelial cells in the loop of Henle epithelium. But we did not observe this feature in our case.

Due to the lack of large-scale epidemiological studies of ADTKD-*UMOD*, the proportion of patients with early onset chronic kidney disease (CKD) or ESRD was still unclear. However, cases have been reported of the onset of ADTKD-*UMOD* in adolescents and even in children (13). *De novo* mutations resulting in ADTKD-UMOD are rare. Previously, many of these families were undiagnosed and uncertain of the cause of inherited kidney disease. Patients with ADTKD-UMOD develop slowly progressive CKD, with a median age of ESKD of 47 years (14). But kidney disease progression is highly variable between and within families. Some individuals may develop ESKD in their 20 s, while others may not require kidney replacement therapy until past 70 years of age (14). As for correlation between genotype and phenotype, a previous study showed that patients with mutations in the EGF domain was at a higher risk of early onset ESRD (15). The early onset of CKD and ESRD may be related to the impaired global protein structure caused by mutations in EGF domain (15). This needs to be confirmed by further cases and experiments in the future.

The known genes causing ADTKD include *UMOD*, *MUC1*, *HNF1B*, *REN*, and *SEC61A1*. And mutations in *UMOD* are the most common type found in up to 3% of monogenic CKD patients (16). *UMOD* gene is located at 16p12.3, and it encodes the uromodulin protein, which is expressed exclusively by epithelial cells of the thick ascending limb of Henle's loop (TALH) and distal convoluted tubule lumen (17). By 2021, a total of 135 *UMOD* mutations have been reported, most of which are located within the 30–300 sites near the N terminus containing the EGF-1, EGF-2, and D8C domains, and 53.8% of all mutations were cysteine substitutions (2). The mutation in our current case is located in the hotspot and is also a cysteine substitution. It has been reported that mutations of disulfide bonds in UMOD can lead to partial endoplasmic reticulum (ER) retention and then trigger ER stress with unfolded protein response, which eventually leads to activation of proinflammatory signals and cell death (18–20).

ADTKD currently lacks treatment options and has a poor prognosis, requiring international cooperation and rare disease organizations to establish a disease registry. Considering the gain-of-toxic-function effect of mutant UMOD accumulated in the ER, decreasing the amount of mutant uromodulin production might be a potential treatment strategy. In the future, gene editing and stem cell research might be explored.

In conclusion, the current case emphasized some lessons for nephrologists to be learned in the era of genetics. This should enhance recognition and correct diagnosis of affected individuals, facilitate genetic counseling, and stimulate research into the underlying pathophysiology.

Ethics statement

This study protocol was reviewed and approved by the Biomedical Research Ethics Committee, Peking University First Hospital, approval number (2018-099). Written informed consent from the patients/participants OR patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written

informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Author contributions

M-SL, YL, and Z-RS collected the data, conceived, and wrote the manuscript. LJ, X-JY, HW, Y-LR, and S-XW provided with the figures. X-JZ revised the manuscript critically for important intellectual content and supervised the research group and gave the final approval of the version to be published. HZ and LY edited the manuscript and gave the final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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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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Case report: Emphysematous pyelonephritis associated with kidney allograft abscess formation

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Emphysematous pyelonephritis (EPN) is a severe, acute necrotizing infection that is defined by the presence of gas in the kidney parenchyma. Multiple case reports have described the radiological findings and clinical course of EPN. Herein, we report on EPN including the histopathological findings in a kidney transplant recipient. Our patient presented with EPN complicated by multiorgan failure and was successfully managed with transplant nephrectomy.

KEYWORDS

immunosuppression, kidney, emphysematous pyelonephritis, kidney transplant recipient, graft nephrectomy

Introduction

Emphysematous pyelonephritis (EPN) is a rare, acute necrotizing kidney infection that is associated with high mortality (1, 2). Immunosuppression and diabetes mellitus are among the major risk factors predisposing to EPN. Herein, we describe a case of a diabetic kidney transplant recipient who presented with EPN associated with extensive cortico-medullary abscess formation requiring transplant nephrectomy.

Case presentation

Our patient is a 49-year-old Caucasian woman who underwent deceased donor kidney transplantation in 2014 for end-stage kidney disease secondary to biopsy-proven diabetic nephropathy. Her medical history is significant for poorly controlled type 2 diabetes mellitus, with her most recent hemoglobin A1c being 11.5%, early post-transplant cytomegalovirus viremia, recurrent urinary tract infections, and mixed

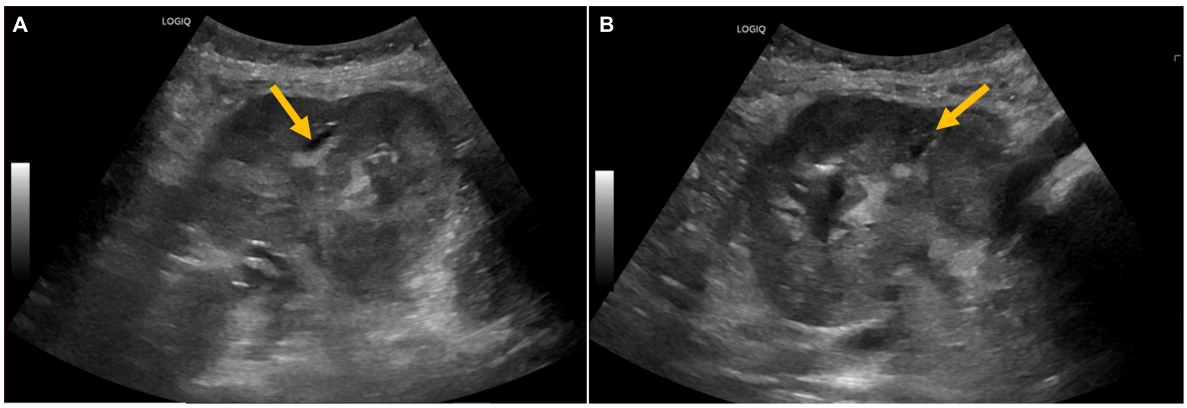

FIGURE 1
(A,B) Ultrasound of the kidney allograft with abnormal echogenicity and ill-defined hyperechoic areas with poor acoustic shadowing, raising suspicion of air in the pelvicalyceal system.

rejection (acute cellular rejection Banff 1B and antibody-mediated rejection) in the setting of donor-specific antibodies against human leukocyte antigen (HLA)-DR53 and HLA-DQ5 in 2019. The patient's rejection episode was attributed to non-adherence with her mycophenolate/tacrolimus regimen suggested by subtherapeutic tacrolimus trough levels. At that time, she was treated with thymoglobulin, intravenous immunoglobulin, and plasmapheresis; however, she sustained chronic allograft insufficiency corresponding to chronic kidney disease stage 4.

She was transferred to our hospital in March 2022 with acute on chronic allograft injury, oligoanuria, abdominal pain, and delirium. At the time of transfer, she was afebrile, her blood pressure was low at 98/59 mm Hg, and her heart rate was 87 beats per minute. Lab results showed serum creatinine of 4.87 mg/dl (eGFR < 15 ml/min/1.73 m^2), white blood cell count of 28,000 cells per cubic millimeter (neutrophil count, 27,000 cells per cubic millimeter), bicarbonate of 15 mmol/L, and anion gap of 16. The patient's urinalysis revealed leukocyturia and microscopic hematuria, and the urine culture grew *Escherichia coli*. The blood cultures were negative.

Ultrasound of the right lower quadrant allograft was suspicious of intraparenchymal gas without any hydronephrosis (**Figures 1A, B**). CT scan of the abdomen showed EPN involving the transplanted kidney with possible perinephric abscesses and thickening of the urinary bladder consistent with cystitis (**Figures 2a–d**). The patient was initiated on vancomycin, ertapenem, and caspofungin, which were later de-escalated to ampicillin-sulbactam. She received fluids and insulin for sepsis and diabetic ketoacidosis. The patient's acute kidney injury episode required initiation of hemodialysis, which was performed with a left internal jugular tunneled dialysis catheter. Based on ongoing abdominal pain and the patient's deteriorating clinical course, a transplant nephrectomy was performed 4 days after admission (**Figures 3a, b**). Kidney allograft tissue culture grew *E. coli* with an antibiogram similar to the urine culture. Pathology of the explant showed extensive cortical and medullary abscess formation with associated tissue destruction (**Figures 4a–c**). There was no evidence of acute cellular or antibody-mediated rejection. The patient's symptoms and leukocytosis subsequently improved. Her immunosuppression was tapered off over one week. She was discharged home 16 days after admission in stable condition and on chronic hemodialysis.

Discussion

Emphysematous pyelonephritis is an acute necrotizing infection of the kidney that is associated with a significant mortality rate of up to 42% (3). EPN is defined by the presence of gas in the kidney parenchyma and/or collecting system (1). The gas is a result of glucose fermentation by Gram-negative bacteria, mainly *E. coli* (56%) and *Klebsiella pneumonia* (22%), which leads to the accumulation of carbon dioxide in the kidney tissue (4, 5). As a result, EPN is strongly associated with diabetes, with more than 80% of episodes occurring in diabetics (6). In addition to hyperglycemia, risk factors for EPN include immunosuppression, female gender, and urinary tract obstruction, most of which were present in our patient (5).

Al-Geizawi et al. proposed a three-stage classification system of EPN specific to kidney allografts (7). According to their classification, gas in the collecting system is stage 1, gas replacing $<50\%$ of kidney parenchyma and with well-controlled sepsis represents stage 2, whereas gas replacing $>50\%$ of parenchyma with extensive spread to the perinephric area or multiple organ failure corresponds to stage 3 (7). According to this classification, our patient fits stage 3, given her multiple organ failure, including acute kidney injury requiring initiation of dialysis and significant mental status changes. Indeed, aligning with our management plan, a recent review reported 100% of

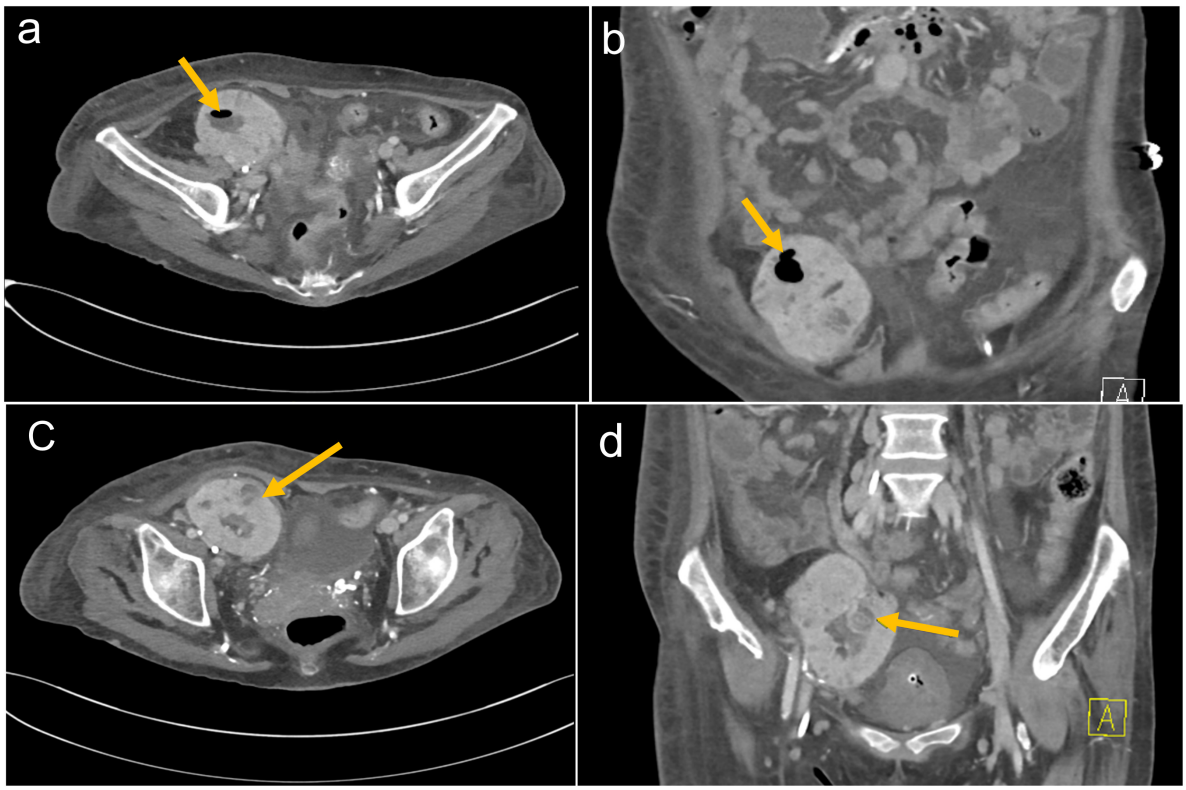

FIGURE 2
(a) Axial and **(b)** coronal CT images of the abdomen demonstrating the right lower quadrant kidney transplant with air in the renal collecting system. **(c)** Axial and **(d)** coronal CT images of the abdomen demonstrating right lower quadrant kidney transplant with loss of cortico-medullary differentiation and developing a complex intraparenchymal fluid collection with adjacent soft tissue perinephric rind. There is debris throughout the collecting system.

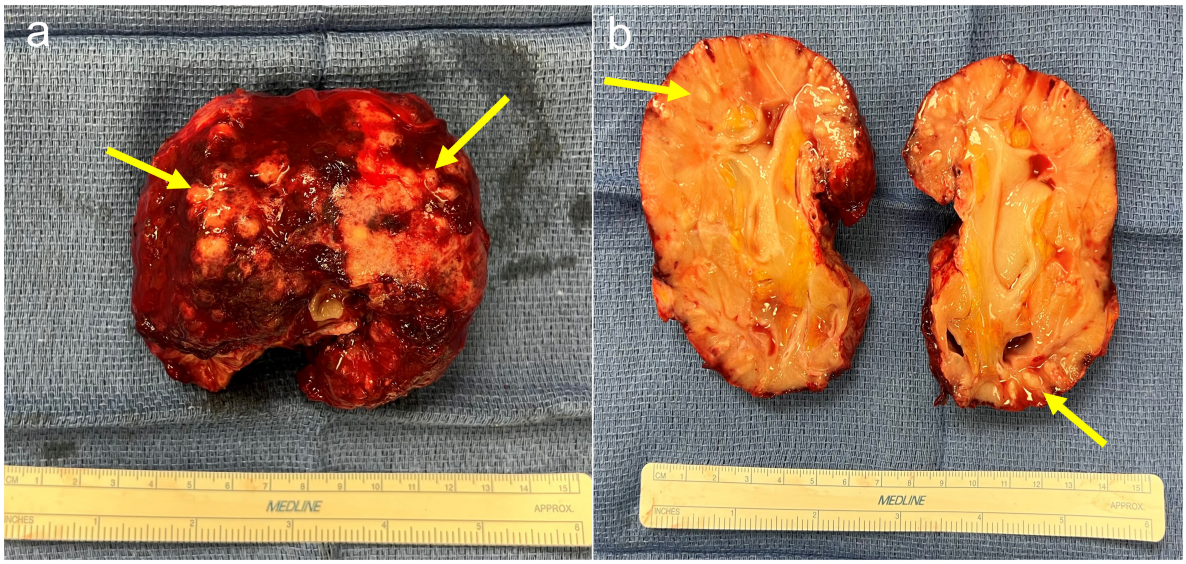

FIGURE 3
(a) Explant of kidney allograft demonstrating multiple abscesses with fibrinous exudate and thick rind material. **(b)** Bisected kidney allograft demonstrating diffusely pale parenchyma and multifocal areas of purulent exudate.

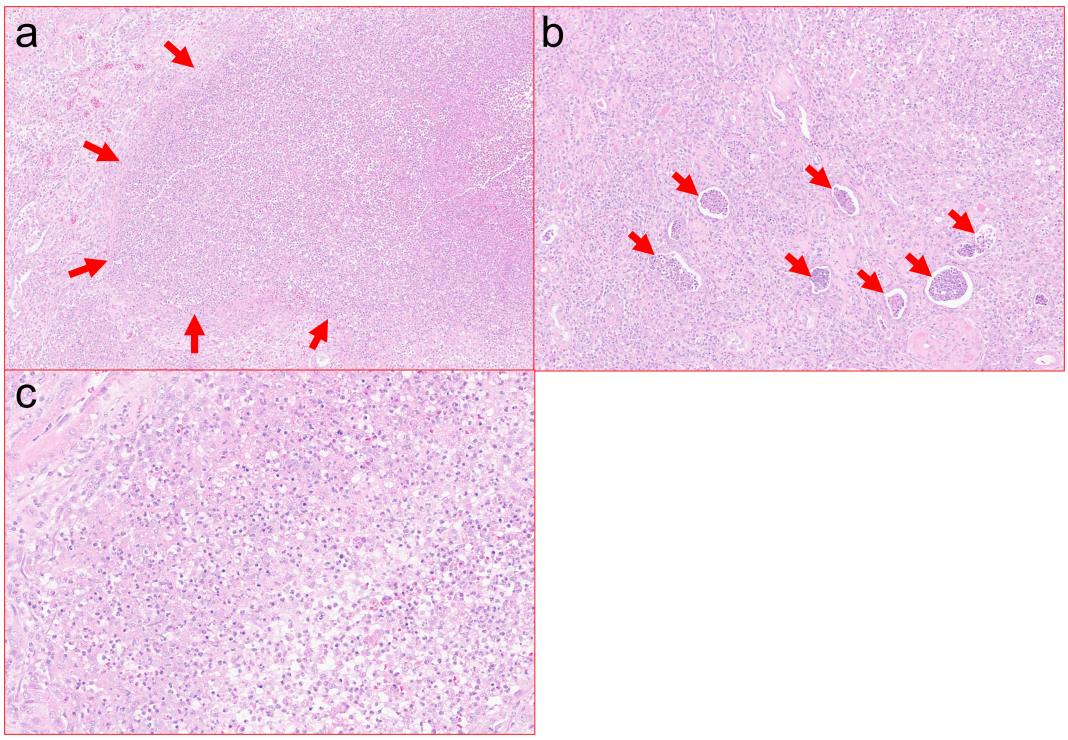

FIGURE 4
(a) Cortical abscess with marked neutrophilic inflammation and associated tissue destruction. Zones of tissue necrosis with abscess, such as pictured here, were present extensively throughout the resection specimen (H&E, 10×). **(b)** Severe interstitial neutrophilic inflammation with associated abundant intratubular abscesses (H&E, 20×). **(c)** High power view of neutrophilic inflammation with associated cellular debris (H&E, 40×).

patients with stage 3 EPN received definitive treatment with transplant nephrectomy. This contrasts with one out of four and two out of nine patients with stages 1 and 2 EPN, respectively, undergoing transplant nephrectomy (4).

Multiple case reports have been published on EPN, mostly with an emphasis on imaging abnormalities. Here, we also report on the histopathological changes in the explant (**Figures 3a, b**, **4a–c**). EPN in our patient was associated with significant neutrophilic inflammation, abscess formation, and tissue destruction leading to an acute deterioration of kidney function requiring dialysis. She had most of the risk factors, including female gender, diabetes, and immunosuppression.

Conclusion

In conclusion, EPN should be considered in patients with poorly controlled diabetes presenting with sepsis, shock, or pyelonephritis. Underlying history of urinary obstruction and/or immune suppression, such as organ transplantation, can be an independent risk factor or further augment the EPN risk posed by uncontrolled diabetes. Prompt initiation of broad-spectrum antimicrobials, urgent abdominal imaging, and surgical consultation for native or allograft nephrectomy can be lifesaving.

Data availability statement

The original contributions presented in this 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 patients OR patients legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

BA contributed to overseeing the work, drafting, and finalizing the manuscript and all the figures. MN contributed to drafting the manuscript and worked on the diagnostic

radiology figures and captions. MR contributed to drafting the manuscript and worked on the pathology figures and captions. HV contributed to drafting the manuscript and providing critical revision of its content. All authors contributed to the article and approved the submitted version.

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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Case report: Importance of early and continuous tocilizumab therapy in nephrotic syndrome associated with idiopathic multicentric Castleman disease: A case series

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Idiopathic multicentric Castleman disease (iMCD) is a systemic and polyclonal lymphoproliferative disease involving multiple organs, including the kidneys, due to the overproduction of interleukin-6 (IL-6). Recently, several reports have suggested that excessive IL-6 actions in iMCD could have a causal relationship with the development of diverse histopathological renal manifestations that cause nephrotic syndrome. However, the treatment for such cases remains unclear. We report a series of three cases of nephrotic syndrome due to iMCD that helps to delineate the importance of early and continuous therapy with the anti-interleukin-6 receptor antibody tocilizumab. First, treatment was suspended for infectious control, and the patient presented with nephrotic syndrome due to diffuse mesangial and endocapillary hypercellularity without immune deposits complicating acute kidney injury. Second, iMCD was treated with prednisolone alone. The patient suddenly developed nephrotic syndrome due to immune-complex glomerulonephritis, not otherwise specified, complicated with acute kidney injury. In the third case, nephrotic syndrome secondary to membranous glomerulonephritis was diagnosed, with a skin rash and IgE antibodies to tocilizumab, and was therefore treated with prednisolone alone. In contrast to the first two cases, the third progressed to end-stage renal disease on hemodialysis. Taken together, this series suggests that clinicians should maintain clinical vigilance for iMCD as a possible underlying component of nephrotic syndrome, since iMCD presents with a variety of renal pathologies.

Prompt initiation and continuous administration of tocilizumab are likely key determinants of renal outcomes in such cases. In particular, when tocilizumab is suspended due to infection or in the perioperative period, consideration of its expeditious resumption should be made, taking into account both the withdrawal period and systemic conditions.

KEYWORDS

idiopathic multicentric Castleman disease, renal pathology, secondary nephrotic syndrome, IL-6 inhibitor, tocilizumab, acute kidney injury, renal replacement therapy

1. Introduction

Castleman's disease (CD) is a polyclonal, non-neoplastic, lymphoproliferative disease first described in the 1950s by Benjamin Castleman (1, 2). From a clinical perspective, the CD can be identified by the distribution of affected lesions. One type of CD is unicentric CD (UCD), in which enlarged lymph nodes are confined to a single area, and multicentric CD (MCD), in which swollen lymph nodes are present in multiple areas (3). MCD is further classified by the presence of human herpesvirus-8 (HHV-8), and HHV-8-negative is defined as idiopathic MCD (iMCD) (4). MCD presents with hepatosplenomegaly, fever, malaise, sweating, anemia, skin rash, edema, pleural effusion, renal involvement, interstitial lung lesions, and arthralgia (3, 5). The onset of such systemic symptoms is acute to subacute in HHV-8-positive MCD but insidious in iMCD (6). Some iMCD cases share a group of clinical characteristics with TAFRO syndrome manifesting as thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O) (7, 8). TAFRO syndrome is often associated with endotheliopathy and adrenalitis (7–9). Notably, the TAFRO subtype of iMCD is defined as TAFRO syndrome with lymph node histopathology consistent with iMCD, and its aggressive clinical behavior includes renal insufficiency and high mortality, particularly in Asian men (8). Importantly, the pathogenesis is thought to be caused by overstimulation of the immune system by interleukin-6 (IL-6) produced in the enlarged lymph nodes (10). Therefore, international evidence-based consensus treatment guidelines for iMCD and TAFRO syndrome recommend glucocorticoid and IL-6 inhibitors (11, 12).

Renal manifestations, including nephrotic syndrome and end-stage renal disease (ESRD), are recognized as important complications of iMCD (11). However, their renal pathology remains unclear. For example, previous studies have shown that patients with iMCD present with diverse histopathological manifestations, including AA renal amyloidosis, IgA nephritis, and thrombotic microangiopathy (13–16). Given that transgenic mice overexpressing IL-6 demonstrated mesangial proliferative glomerulonephritis (17), and IL-6 inhibition by tocilizumab improved nephrotic syndrome due to membranous glomerulonephritis and renal amyloidosis in iMCD (18, 19), excessive IL-6 secretion likely plays an important role in the development of renal complications and systemic manifestations. However, the effects of initiation timing, suspension, or termination of the IL-6 inhibitor tocilizumab on renal outcomes in iMCD remain unknown. Herein, we report three cases of iMCD with nephrotic syndrome, demonstrating that prompt and continuous tocilizumab administration may be an important factor in the management of nephrotic syndrome and renal prognosis.

2. Case descriptions

2.1. Case 1

A 53-year-old Japanese woman with iMCD and type 2 diabetes was admitted to our hospital for the treatment of cellulitis and acute kidney injury (AKI). At the age of 51 years, the patient had polyclonal hypergammaglobulinemia (IgG, 3,219 mg/dl; IgA, 659 mg/dl; IgM, 151 mg/dl), elevated levels of IL-6 (38.5 pg/ml) and soluble interleukin-2 receptor (912 U/mL), anemia (Hb 8.5 g/dl) (**Table 1**), and multiple enlarged lymph nodes. She underwent a lymph node biopsy in the right external iliac region and was diagnosed with iMCD (**Figure 1A**). Because the patient had type 2 diabetes mellitus on insulin therapy, she initially received 8 mg/kg of tocilizumab alone every 3 weeks, which was later decreased to every 5 weeks. On admission, her right lower leg appeared swollen, red, painful, and warm. She was diagnosed with cellulitis, and tocilizumab was discontinued for infection control. Her serum creatinine and 24-h urinary protein levels increased to 5.0 mg/dl and 18.1 g/day, respectively, with baselines of 0.9 mg/dl and 0.6 g/day, respectively. The selectivity index was 0.48. Inflammatory markers including peak C-reactive protein (CRP) level, D-dimer, and ferritin were 25.19 mg/dl, 30.2 μg/ml, and 193 ng/ml, respectively (**Table 1**). Renal biopsy identified 10 glomeruli, of which five were globally sclerosed. The remaining glomeruli showed diffuse mesangial hypercellularity, with focal endocapillary hypercellularity (**Figure 1B**). Congo red staining results were negative. Immunofluorescence microscopy revealed no remarkable staining of the glomeruli. Electron

TABLE 1 Clinical markers of the cases.

	Case 1	Case 2	Case 3	Normal range
Sex	Female	Male	Male	
Age (years old)	53	60	58	
Organ involvement	Kidney	Kidney	Kidney	
Urinary protein (g/24 h)	18.1	15.7	3.5	
Serum Creatinine (mg/dL)	5	1.92	2	(0.65–1.07)
IL-6 (pg/ml)	38.5	13.5	639	(<7)
Peak C-reactive protein (mg/dL)	25.19	2.67	9.48	(0–0.14)
Immunoglobulin G (mg/dL)	3,219	3,201	8,039	(870–1,700)
Albumin (g/dL)	2.2	2.1	2.4	(4.1–5.1)
Hemoglobin (g/dl)	8.5	6.3	10.3	(13.7–16.8)
Platelets (/μL)	28.4×10^4	19.9×10^4	28.7×10^4	(15.8–34.8)
Ferritin (ng/mL)	193	298	117	(8–129)
D-dimer (μg/mL)	30.2	9	0.5	(0–1)
Soluble interleukin-2 receptor (U/mL)	912	1,195	2,043	(142–500)

microscopy demonstrated subendothelial widening with neo-densa and thickening of the glomerular basement membrane partly due to diabetes (Figure 1C). These features of glomerular injury are considered to represent endothelial injury, which is likely associated with iMCD. Therefore, tocilizumab (8 mg/kg) was resumed, leading to significant improvements in CRP levels, proteinuria, and kidney function. She was discharged after complete healing of cellulitis. Two months later, her serum creatinine and 24-h urinary protein levels had declined to 1.54 mg/dl and 1.6 g/day, respectively (Figure 1D).

2.2. Case 2

A 60-year-old Japanese man with iMCD was admitted to our hospital with nephrotic proteinuria, reduced renal function, and anemia. At the age of 59 years, he presented with multiple enlarged lymph nodes. A biopsy of the right axilla revealed plasma cell infiltration, leading to a diagnosis of iMCD (Figure 2A). The patient had polyclonal hypergammaglobulinemia (IgG, 3,201 mg/dl; IgA, 487 mg/dl; IgM, 139 mg/dl), and high levels of IL-6 (13.5 pg/ml) and soluble interleukin-2 receptor (1,195 U/mL). In addition, peak CRP level was 2.67 mg/dl (Table 1). He was administered 40 mg of oral prednisolone daily, which was tapered. At the age of 60 years, he noticed progressive pretibial edema and an increase in body weight of 9 kg over 2 months. Laboratory investigations indicated AKI with a serum creatinine of 1.92 mg/dl and anemia with a hemoglobin of 6.3 g/dl. His 24-h urinary protein was 15.7 g/day and serum D-dimer was 9.0 μg/ml (Table 1). Renal biopsy revealed focal endo- and extra-capillary hypercellularity with hyaline deposits (Figure 2B). Tubular injury with red blood cell casts was also observed (Figure 2C). Immunofluorescence microscopy revealed 1 + to 2 + granular mesangial and capillary staining for IgG, IgA, IgM, C1q, and C3, corresponding to hyaline deposits (Figure 2D). Although large hyaline deposits were not observed by electron microscopy, small mesangial deposits were identified (Figure 2E). Systemic lupus nephritis was ruled out because we detected no apparent clinical manifestations of lupus, such as oral ulcers, subacute cutaneous or discoid lupus, and joint pain, and found a normal ds-DNA level (5.8 IU/ml) with a negative antinuclear antibody test and normal complement levels (C3 component 77 mg/dL, C4 component 21 mg/dL, respectively). In addition, monoclonal gammopathy was excluded based on a normal kappa/lambda ratio (0.89) and serum immunofixation electrophoresis. The patient was diagnosed with immune-complex glomerulonephritis, not otherwise specified, associated with iMCD. He was started on tocilizumab (8 mg/kg) every 2 weeks, plus 10 mg of prednisolone daily. Serum creatinine, CRP, and urinary protein excretion levels improved immediately. His 24-h urinary protein was 0.3 g/day at discharge. The patient remained in remission (Figure 2F).

2.3. Case 3

A 58-year-old Japanese man with iMCD and ESRD with nephrotic proteinuria was hospitalized for hemodialysis. At the age of 44 years, he presented with multiple enlarged lymph nodes, and a left axillary biopsy revealed iMCD (Figure 3A). His 24-h urinary protein was 1.5 g/day. Renal biopsy revealed a slight mesangial expansion and focal segmental glomerular sclerosis with podocyte hyperplasia (Figure 3B). Electron microscopy revealed only a few subepithelial deposits, which suggested atypical membranous glomerulonephritis (Figure 3C). The patient was monitored without therapy because he was asymptomatic. At the age of 46 years, laboratory investigations showed hemoglobin 10.3 g/dL, CRP 9.48 mg/L, polyclonal hypergammaglobulinemia (IgG, 8,039 mg/dl; IgA, 454 mg/dl; IgM, 146 mg/dl), IL-6 639 pg/ml, and 24-h urinary protein 3.5 g/day (Table 1). Although tocilizumab was initiated, the skin rash appeared soon after treatment initiation, and IgE antibodies to tocilizumab were detected. Therefore, treatment was stopped, and prednisolone monotherapy was initiated. However, the CRP level remained slightly elevated at approximately 2–3 mg/dl. As the degree of proteinuria increased, renal function gradually deteriorated. We suggested a rechallenge with tocilizumab; however, the patient did not consent. At the age of 57 years, 24-h urinary protein levels further increased to 6.948 g/day. Although

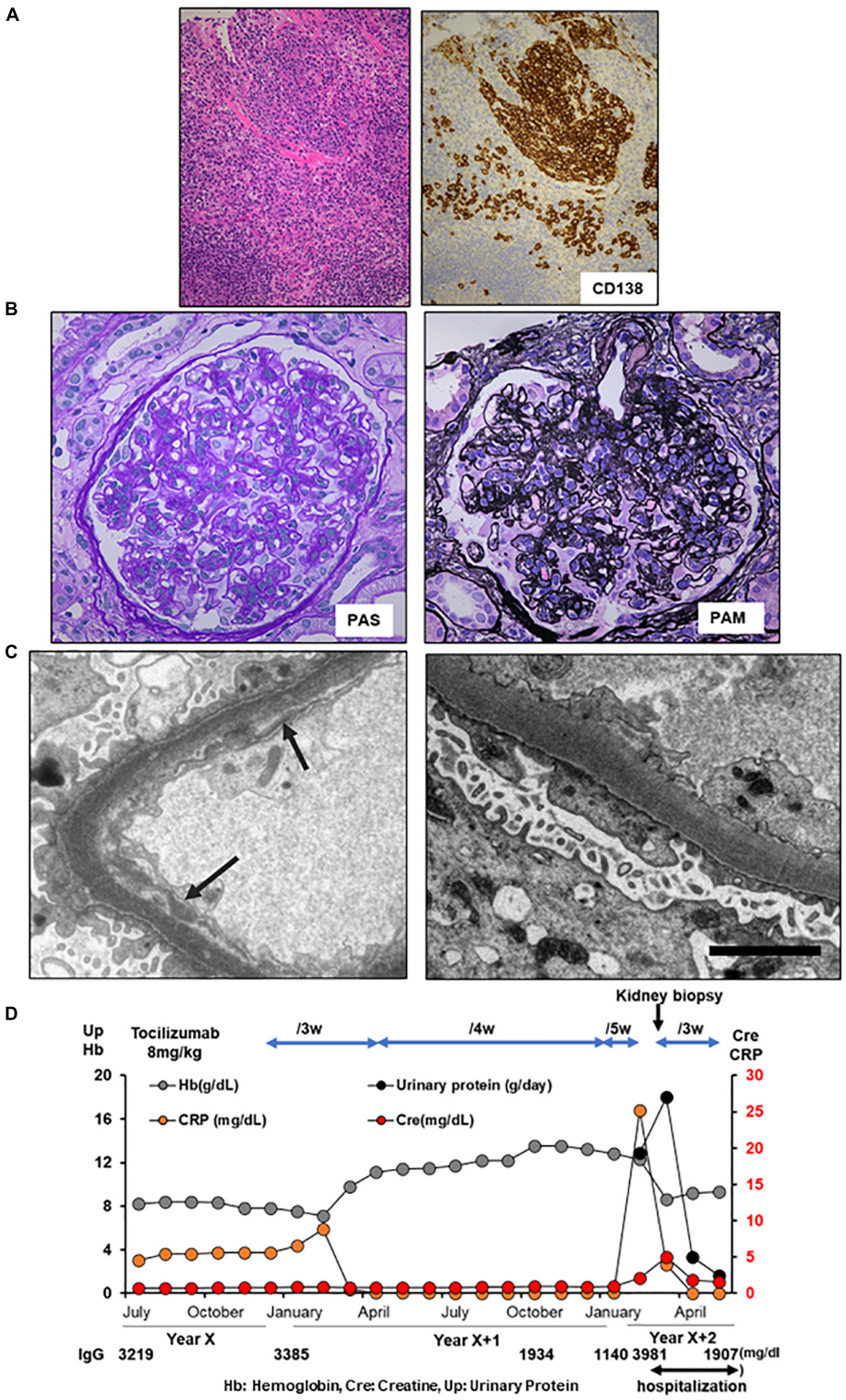

FIGURE 1
Histology and time course for Case 1. **(A)** Light microscopy of the external iliac lymph node exhibiting follicular hyperplasia (left lower) and infiltration by $CD138^{+}$ plasma cells. **(B,C)** Renal biopsy. **(B)** Light micrograph showing diffuse mesangial and endocapillary hypercellularity. **(C)** Electron micrograph showing subendothelial widening with neo-densa (left, silver impregnation) and glomerular basement membrane thickening (right). Arrows indicate argyrophilic neo-densa. Scale bar, 2.5 μm. PAS: Periodic acid–Schiff. PAM: Periodic acid methenamine. **(D)** Clinical time course of Case 1. Hb, hemoglobin, Cre, creatine, Up, urinary protein.

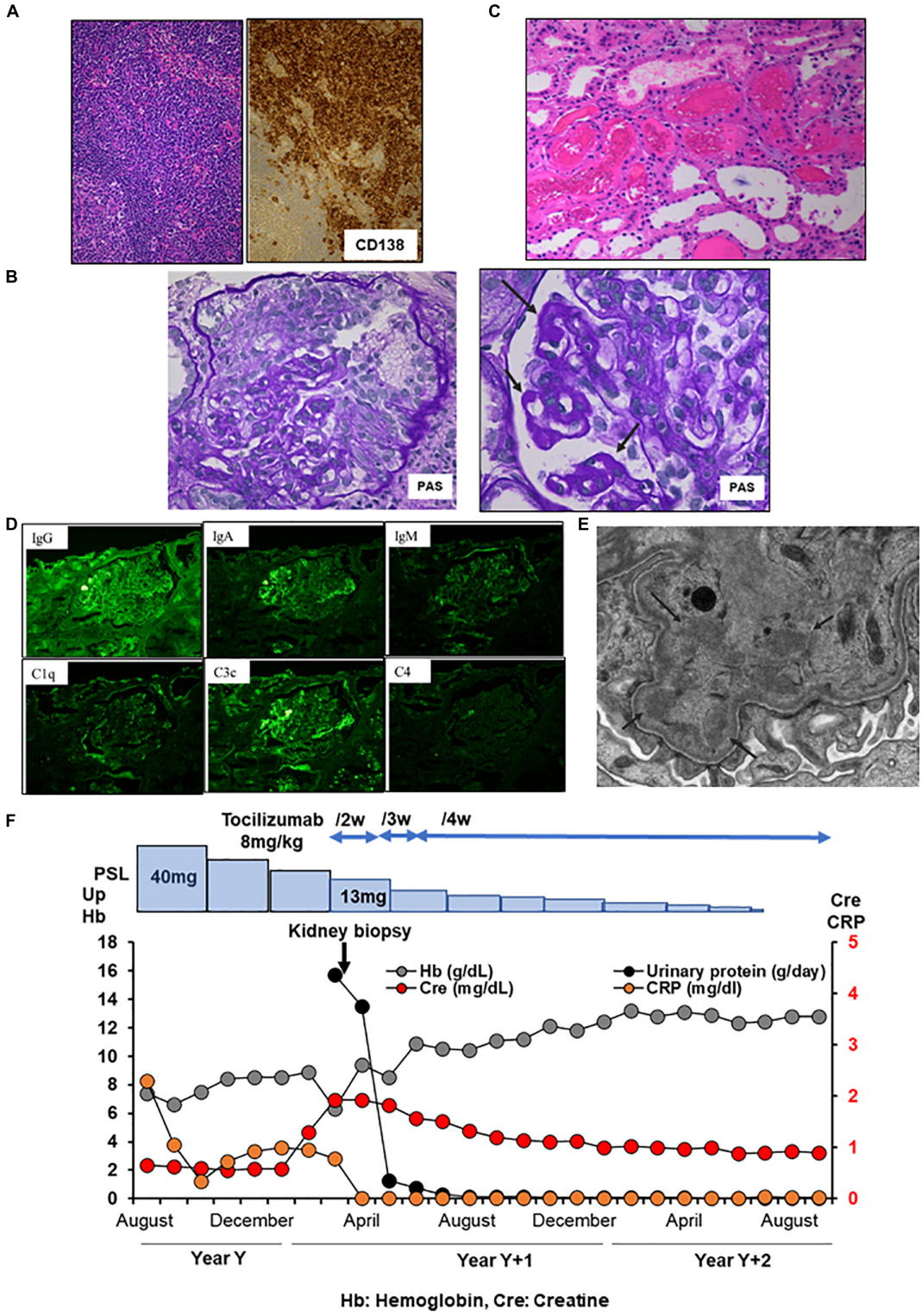

FIGURE 2
Histology and time course for Case 2. **(A)** Light micrograph of the lymph node showing follicular hyperplasia (left lower) and infiltration by plasma cells which are positive for CD 138. **(B–E)** Renal biopsy. **(B)** Light micrograph showing focal endo- and extra-capillary hypercellularity with hyaline deposits (arrows). **(C)** Tubular injury with red blood cell casts is observed. **(D)** Immunofluorescence micrograph showing granular mesangial and capillary staining for IgG, IgA, IgM, C1q, and C3. **(E)** Electron micrograph showing mesangial deposits (arrows). PAS: Periodic acid–Schiff. PAM: Periodic acid methenamine. **(F)** Clinical time course of Case 2. Hb, hemoglobin; Cre, creatine; Up, urinary protein.

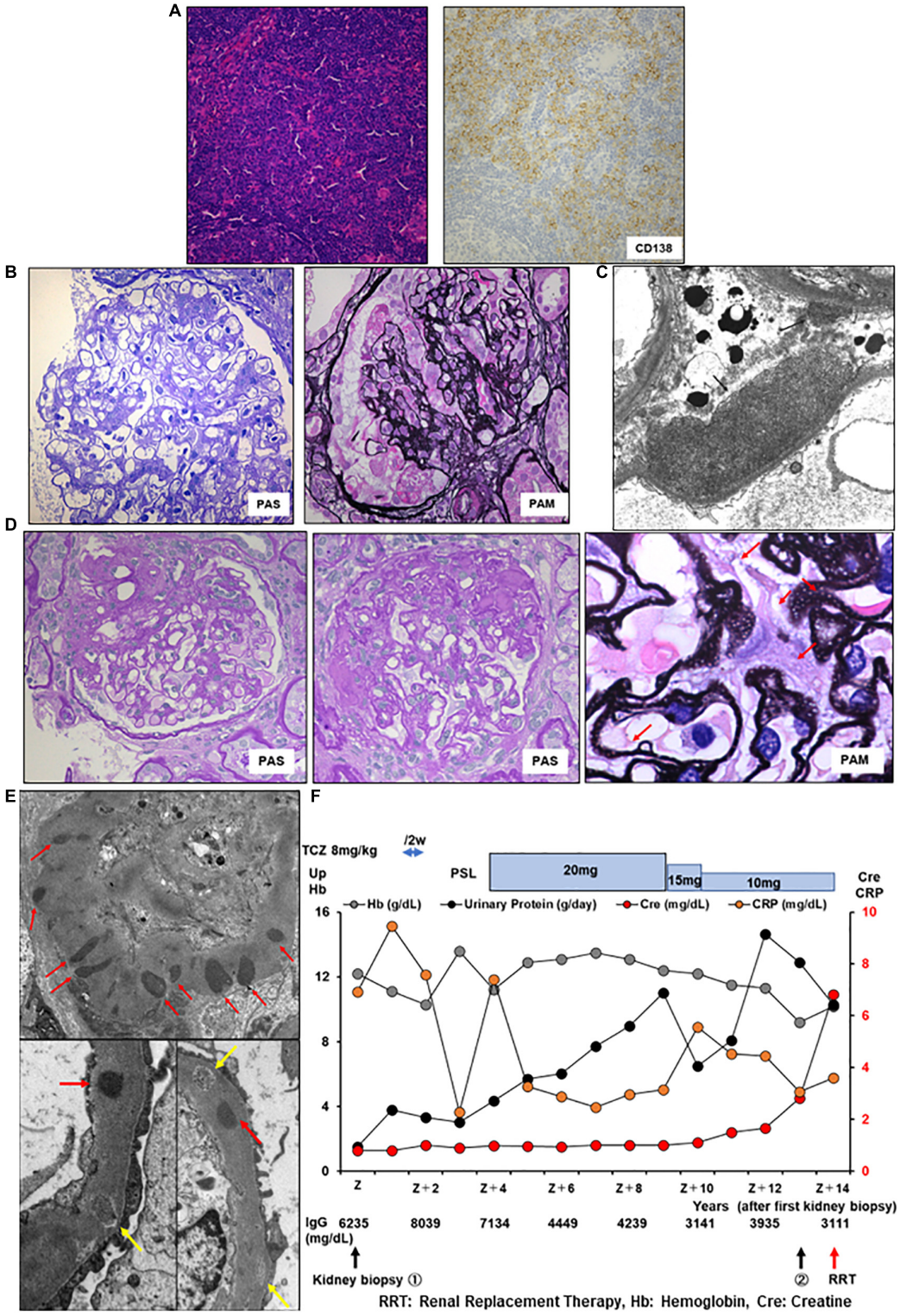

FIGURE 3
Histology and time course for Case 3. **(A)** Light micrograph of the lymph node showing follicular hyperplasia (left lower) and infiltration by plasma cells which are positive for CD 138. **(B,C)** First renal biopsy. **(B)** Light micrograph showing slight mesangial expansion and focal segmental glomerular sclerosis. **(C)** Electron micrograph showing focal subepithelial deposits (arrows). **(D,E)** Second renal biopsy. **(D)** Light micrograph showing focal global and segmental sclerosis with diffuse glomerular basement membrane lucencies (red arrows). **(E)** Electron micrograph showing subepithelial and intramembranous deposits (red arrows). Some of the intramembranous deposits are electron-lucent and granular appearance (yellow arrows). PAS: Periodic acid–Schiff. PAM: Periodic acid methenamine. **(F)** Clinical time course of Case 3. Hb, hemoglobin; Cre, creatine; Up, urinary protein; RRT, renal replacement therapy.

the selectivity index was 0.36, the patient underwent a second renal biopsy. Light microscopy revealed focal global and segmental sclerosis with diffuse glomerular basement membrane lucency on sliver staining (**Figure 3D**). Congo red staining results were negative. Electron microscopy revealed the presence of subepithelial and intramembranous deposits (**Figure 3E**). The patient was diagnosed with membranous glomerulonephritis associated with iMCD. His renal function further diminished, and he required renal replacement therapy (**Figure 3F**).

3. Discussion

Our case series demonstrated that (1) iMCD should be acknowledged as an underlying cause of nephrotic syndrome, albeit rare, and (2) immediate and uninterrupted tocilizumab therapy is likely essential for the management of iMCD-associated renal complications, especially nephrotic syndrome. In addition, our cases with hypergammaglobulinemia without thrombocytopenia, anasarca, or organomegaly could be categorized as non-TAFRO iMCD (20).

Many cases of CD are associated with renal dysfunction (21–23) and MCD is clinically characterized by renal dysfunction (24). However, renal pathology in MCD is diverse; a recent investigation of 64 patients and previous case reports revealed that the renal pathologies underlying renal derangements included amyloidosis, membranoproliferative glomerulonephritis, thrombotic microangiopathy, membranous glomerulonephritis, minimal change disease, and mesangial proliferative glomerulonephritis (18, 19, 25–28). IgA nephropathy (29) and interstitial nephritis (30, 31) have also been reported. Although renal function in MCD is reportedly an important prognostic factor for survival (32), MCD is not well recognized as a cause of renal dysfunction, especially secondary nephrotic syndrome, probably because of the highly diverse renal pathological findings.

Our three cases of iMCD presenting with nephrotic syndrome consistently displayed diverse renal pathologies: glomerular endothelial injury, immune-complex glomerulonephritis, and membranous glomerulonephritis. The mechanism(s) responsible for the multiple renal pathologies that cause nephrotic syndrome in iMCD remains unclear but may involve the overproduction of IL-6 in the affected lymph nodes (33). Interestingly, it was reported that high circulating levels of IL-6 might contribute to the glomerular loss of vascular endothelial growth factor (VEGF) expression in iMCD (34), thereby triggering renal thrombotic microangiopathy (33, 35), as in Case 1. Podocyte-specific *Vegf*-knockout mice exhibit glomerular endothelial damage (36, 37). In addition, high levels of IL-6 are known to promote B cell activation, which in turn induces glomerulonephritis with immune complex (22), as in Case 2.

As the overproduction of IL-6 could be involved in the development of renal complications in iMCD, it has been reported that IL-6 inhibitors are effective for prevention and treatment of iMCD-associated nephrotic syndrome (18, 19, 38, 39). Although a previous report showed that nephrotic syndrome in iMCD was relieved by steroids alone (40), international, evidence-based, consensus treatment guidelines for iMCD recommend treatment with IL-6 inhibitors siltuximab or tocilizumab, regardless of disease severity. For severe iMCD, based on the Castleman Disease Collaborative Network severity classification, IL-6 inhibitor plus glucocorticoid is recommended (11). As we experienced in Case 2, given that a possible causal relationship between excessive IL-6 production and renal complications, including nephrotic syndrome, is established, we strongly recommend introducing tocilizumab from the induction phase of treatment for iMCD.

In contrast, over the course of iMCD treatment, clinicians are required to suspend or discontinue tocilizumab because of side effects such as infection and allergic reactions, as in cases 1 and 3, respectively. Although lifelong administration of tocilizumab is important for control (41, 42), infection is a crucial complication of IL-6 inhibitors; 7% of patients with MCD receiving tocilizumab develop cellulitis (34). A previous case report revealed that an 8-week temporary cessation after long-term administration of tocilizumab due to orthopedic surgery led to a relapse of iMCD (42). Importantly, 1 μg/mL of serum-free tocilizumab, which can be maintained over 4 weeks after a single administration of 8 mg/kg tocilizumab, is the lowest concentration required to block IL-6 signaling (43, 44). Indeed, our Case 1 demonstrated that a 6-week suspension of tocilizumab due to infection caused nephrotic syndrome. Taken together, we speculate that tocilizumab should be carefully reintroduced within 4 weeks based on the severity of the infection.

Case 3 also illustrates the important role of tocilizumab in protecting renal function in iMCD. The patient was allergic to tocilizumab and had been receiving prednisolone monotherapy for approximately 12 years. A case report showed that nephrotic syndrome in iMCD was successfully resolved after corticosteroid monotherapy (40). However, our patient was in the nephrotic range of proteinuria due to secondary membranous glomerulonephritis, with a CRP level of approximately 3 mg/dl, ultimately resulting in ESRD requiring hemodialysis. Importantly, a recent case report demonstrated that an Asian male with the TAFRO subtype of iMCD required hemodialysis twice and could withdraw from dialysis by initiating IL-6 blockers (45). To the best of our knowledge, this is the first case report of chronic maintenance renal replacement therapy for iMCD. Together, these results demonstrate that

tocilizumab may be a key determinant of renal prognosis in iMCD, especially in patients with nephrotic syndrome.

Our case series demonstrates the importance of recognizing iMCD as a possible causative disease of secondary nephrotic syndrome with various histopathological findings, which could result in ESRD on dialysis, albeit rarely. Our cases also support the contention that early and continuous administration of tocilizumab may not only be effective in controlling iMCD disease activity but also in preventing the onset and progression of associated renal complications, such as nephrotic syndrome. Specifically, when tocilizumab should be suspended due to infection or the perioperative period, expediting the resumption of tocilizumab is required, taking into account its withdrawal period as well as systemic conditions.

Data availability statement

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

Ethics statement

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

Author contributions

DK and SY wrote the manuscript. All authors took clinical care of the patient and have read and approved the final manuscript.

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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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Case report: 11 years on hemodialysis with a 4-year-old baby girl: A success story

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Despite advances in clinical management and dialysis care, the outcome of unplanned pregnancy in women on maintenance hemodialysis (MHD) remains a difficult journey for the patient, fetus, and healthcare staff, particularly in low-resource countries. We report the successful outcome of a pregnancy in an anuric woman on twice-weekly maintenance hemodialysis for chronic glomerulonephritis since November 2012 in Cameroon. She was discovered pregnant at 18 weeks of gestation. The pregnancy was maintained until 36 weeks when a healthy 2,270 g female baby was delivered by elective cesarean section for tight nuchal cords and intrauterine growth retardation. The mother's post-partum period was uneventful. Except for hypoglycemia shortly after birth, the baby was fine. The patient is still on hemodialysis after 4 years, and the child is healthy and attending school.

KEYWORDS

pregnancy, outcome, hemodialysis (HD), Cameroon (Sub-Saharan Africa), Bamenda

Background

Pregnancy on maintenance hemodialysis (MHD) is shifting from being an exception to being a rare, but not an impossible event (1). However, this remains exceptional in resource-limited settings where dialysis adequacy is unachievable due to inadequate funding, absence of health coverage, and limited access to both dialysis and corrective therapies for end-stage kidney disease (ESKD) (2). To date, the conception and successful outcome of these pregnancies are much more frequent when the patients have a residual kidney function, a shorter HD vintage, and adequate dialysis efficiency and pharmacologic treatment (1). However, when pregnancy occurs under such precarious conditions, it becomes a very challenging journey for the patient, the fetus, and the healthcare staff. Despite an increasing number of successful pregnancies in developed countries (1, 3–5), there are sparse reports of successful pregnancies in women undergoing MHD in Sub-Saharan Africa where dialysis is heavily self-funded (1, 2).

In Cameroon, Ashuntantang et al. reported in 2014 a conception rate of 7.14% over 11 years in a series of 84 women of childbearing age undergoing MHD (2). To date, only two cases of successful pregnancies in women on MHD have been reported in the country (2, 6). These two successful cases have been reported in first-category hospitals in patients on hemodialysis for less than 24 months with residual kidney function. We, hereby, report the first successful pregnancy in an anuric lady after 7 years on a twice-weekly MHD in a third-category hospital in Cameroon. The patient provided written consent for publication of the case.

Case presentation

Ms. X was a 29-year-old woman in 2017, who had been on MHD since November 2010 for severe uremic encephalopathy secondary to end-stage kidney disease, presumed to be secondary to hepatitis B virus-related glomerulonephritis. She/the patient became anuric 3 years after the initiation of dialysis. Her dialysis routine consisted of two HD sessions of 4 h weekly (on Wednesday and Saturday; occasionally once a week during stock-outs of HD supplies), using bicarbonate dialysate and polysulfone dialyzer with a surface area of 1.8 m^2. HD was performed using the Fresenius 4008S generator (Fresenius Medical Care Homburg, Germany). Her regular medications included amlodipine 10 mg/day and calcium carbonate. She occasionally received alfacalcidol 0.25 μg three times per week depending on the availability of funds. She received frequent blood transfusions for anemia correction and became hepatitis C positive after 3 years on HD. She was single, nulliparous, had never been pregnant, and had a very irregular menstrual cycle for the past 2 years.

She consulted on 20 September 2017 for a distended and painless abdomen of 8 weeks duration. Abdominal distention had been progressive and was associated with an increase in food cravings and hunger pangs. Her ongoing medications were as usual. Further questioning and analysis of her HD record revealed an unusual increase in interdialytic weight gain of 2 kg and frequent intradialytic hypotension within the past 3 months before the consultation. On examination, blood pressure (BP) was 125/82 mmHg and weight was 56.75 kg. Abdominal examination revealed an increased uterus with a symphyseal-fundal height of 15 cm. Pelvic ultrasonography confirmed a live singleton intrauterine pregnancy estimated at 18 weeks of gestation with normal amniotic fluid volume. The biochemical work-up of the patient at the diagnosis of pregnancy is reported in Table 1. She/the patient was extensively counseled about the challenges of pregnancy on MHD; however, she opted to keep the pregnancy. According to previous reports on management guidance, changes were made in her dialysis care (5, 7). We then modified the HD regimen: the number of HD sessions was increased from 2 to 4 per week and the duration from 4 to 5 h each up to the 34th week of gestation, and then from 4 to 5 sessions of 5 h per week (25 h/week) till delivery. The surface area of the dialyzer was reduced to 1.5 m^2 and the maximum blood flow rate and ultrafiltration rate were set at 250 ml/min and 400 ml/h, respectively. We introduced slow ultrafiltration to achieve a weight gain of 0.5 kg every fortnight and a target post-dialysis systolic blood pressure between 110 and 130 mmHg and diastolic between 80 and 90 mmHg (see Figure 1). Standard heparin was continued till 34 weeks of gestation after which it was substituted with enoxaparin to minimize the risk of hemorrhage. She was placed on 100 mg of aspirin daily and epoetin beta three times per week with the dose adjusted to maintain the maternal hemoglobin at 11–12 mg/dl. Other drugs introduced included: 100,000 UI of native vitamin D every 2 months, 500 mg of vitamin C twice per week, intravenous vitamin B complex at end of every HD session, 5 mg of folic acid daily, and 100 mg of intravenous iron sucrose weekly. Amlodipine was substituted for nicardipine and she continued calcium carbonate but between meals this time. She was also placed on a weekly dose of three tablets of a fixed combination of sulfadoxine 500 mg and pyrimethamine 25 mg for malaria prophylaxis as per standard local antenatal care practice. We did not limit the patient's dietary intake except for salt restrictions, and the patient was encouraged to increase the intake of dairy products and animal protein to prevent hypophosphatemia in the absence of phosphorus tablets. Obstetric care consisted of 2 weekly standard care similar to non-HD pregnant women. Serial obstetric ultrasonography was performed monthly to assess fetal morphology and growth, placental blood flow, and amniotic fluid volume (Table 2). Pre-hemodialysis full blood count, serum creatinine, blood urea, sodium, potassium, phosphorous, and calcium were done weekly, while plasma uric acid and C-reactive protein were monitored monthly (see Figure 2). To attain these objectives, non-governmental organizations, individual sponsors, and the hospital provided material and financial assistance to cover all the costs of care. The evolution was uneventful, but a persistent increase in BP above the target at 28 weeks of gestation led to the addition of alpha-methyldopa (250 mg twice daily). Despite this, the BP continued rising without features of pre-eclampsia. Labetalol 400 mg/day was then added (Figure 1). Despite malaria prophylaxis, she had an episode of malaria at 25 weeks of gestation, which was successfully treated with quinine protocol.

The patient was admitted at 36 weeks for elective cesarean section with the indication being tight nuchal cords and intrauterine growth retardation. On 24 January 2018, she underwent a cesarean section under spinal anesthesia with 10 mg of hyperbaric bupivacaine, and a 2,270 g female baby with an Apgar score of 9 at 1 min and 10 at 5 min was delivered 10 min after the beginning of surgery. The estimated blood loss was less than 200 ml. After the surgery, the mother was stable but for a blood pressure of 148/108 mmHg. She was then transferred to the intensive care unit (ICU). Her post-operative

TABLE 1 Initial biochemical work-up of mother.

Initial biological work-up	26/9/2017 (week 19)	Reference/norme
WBC (/mm^3)	6,000	3,500–10,000
Hemoglobin (g/dl)	10.3	12–16
Platelets (/mm^3)	189,000	150,000–440,000
CRP (mg/l)	20	<6
Predialysis urea (mg/dl)	87	15–45
Predialysis creatinine (mg/dl)	7.9	0.5–1.1
Sodium (mmol/l)	139	137–151
Potassium (mmol/l)	6.4	3.5–5.8
Calcium (mg/dl)	8.56	8.1–10.4
Phosphorus (mg/dl)	2.3	2.7–4.5
Uric acid (mg/dl)	4.8	2.5–6
AST	27.6	13–31
ALT	20.6	7–35
Prothrombin time (%)	98	70–100
HIV	Negative	Negative
AgHBs	Positive	Negative
AgHBe	Negative	Negative
AbHBc	Positive	Negative
HCV ab	Positive	Negative
VDRL	Negative	Negative
TPHA	Negative	Negative
Toxoplasmosis IG g (UI/L)	10	

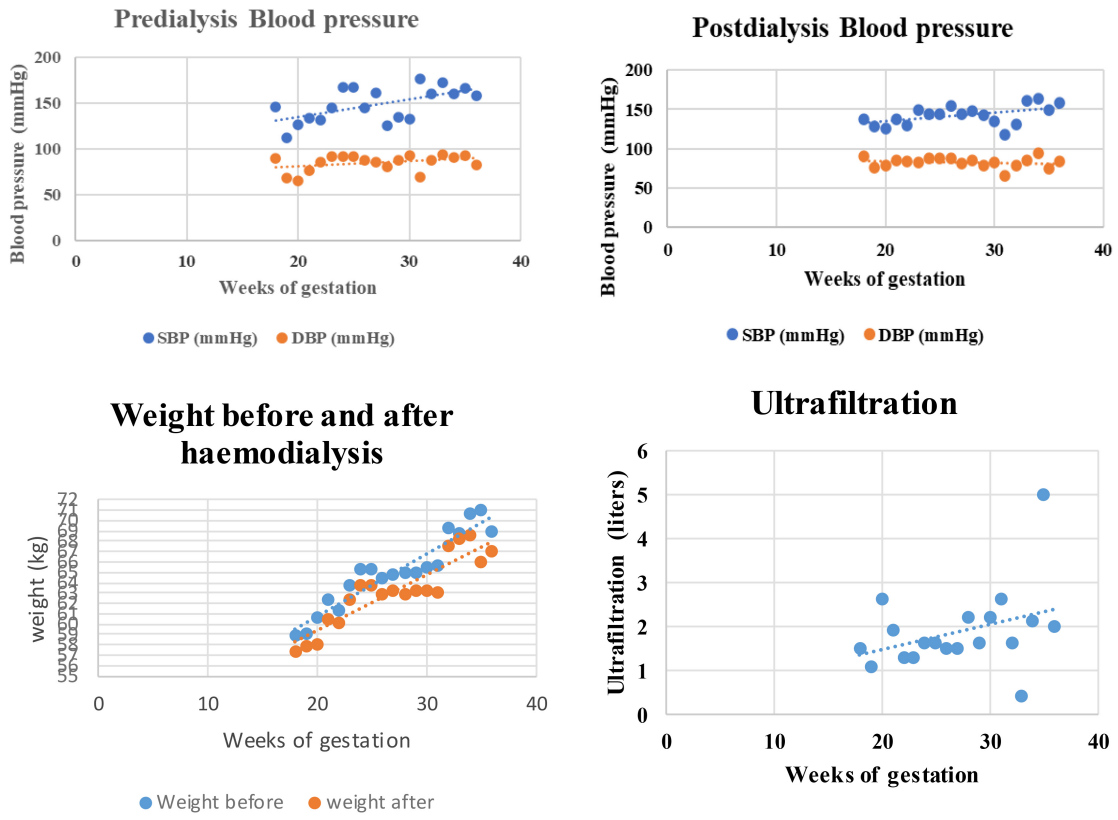

FIGURE 1
Blood pressure, weight, and ultrafiltration with the gestational age of the mother.

TABLE 2 Ultrasound follow-up of the mother.

Variable	20/9/2017	19/10/2017	28/12/2017	19/1/2018
Estimation gestational age	18 wk+1 d	22 wk+3 d	30 wk+4 d	34 wk+1 d
Weight (grams)	222	485	1,541	2,340
Resistivity index	Normal	Normal	Normal	Normal+tight nuchal cords
Amniotic fluid	Normal	Normal	Normal	Normal
Foetal heartbeat	147	155	139	143
Morphology		Normal	Normal	Normal
Presentation			Cephalic	
Placenta			Grade 2 posterior	Grade 2 posterior

course was uneventful, and on the second day post-operatively, she resumed her pre-pregnancy hemodialysis schedule of 4-h sessions twice a week. She was discharged home on the 10th day post-operatively and is still on hemodialysis 4 years after. For the neonate, she was admitted to the neonatal care unit immediately after delivery where she presented with hypoglycemia of 60 mg/dl. No polyuria, no signs of dehydration, and no morphological malformations were observed. She was then placed on glucose 10%, calcium gluconate, and parenteral antibiotics. She also received hepatitis B immune globulins and a vaccine against hepatitis B to prevent maternal–fetal transmission. Due to the risk of maternal–fetal transmission of hepatitis B, the baby was exclusively fed with artificial milk. The baby evolved well and was discharged home on day 7.

To this date, the child has never been hospitalized. She was fed on commercial breast milk substitutes from birth till 5 months. Gruel and cereals fortified with milk were introduced from 6 to 8 months. The semi-solid adult food was commenced from the ninth month, and she was fed 4–5 times a day with at least two milk drinks in her diet. Growth monitoring showed catch-up growth with the progressive acceleration of physical anthropometric parameters indicative of normal growth (see Figure 3). The developmental milestones acquisition was adequate for the age. She was followed up regularly by the pediatrician and reported five episodes of acute febrile illness with cough treated as an outpatient for acute uncomplicated respiratory tract infection. At 46 months, her blood pressure, renal ultrasonography, and laboratory results, including a full blood count, blood chemistry, serum creatinine, and urine dipstick, were essentially normal. AgHBs serology was negative (see Table 3).

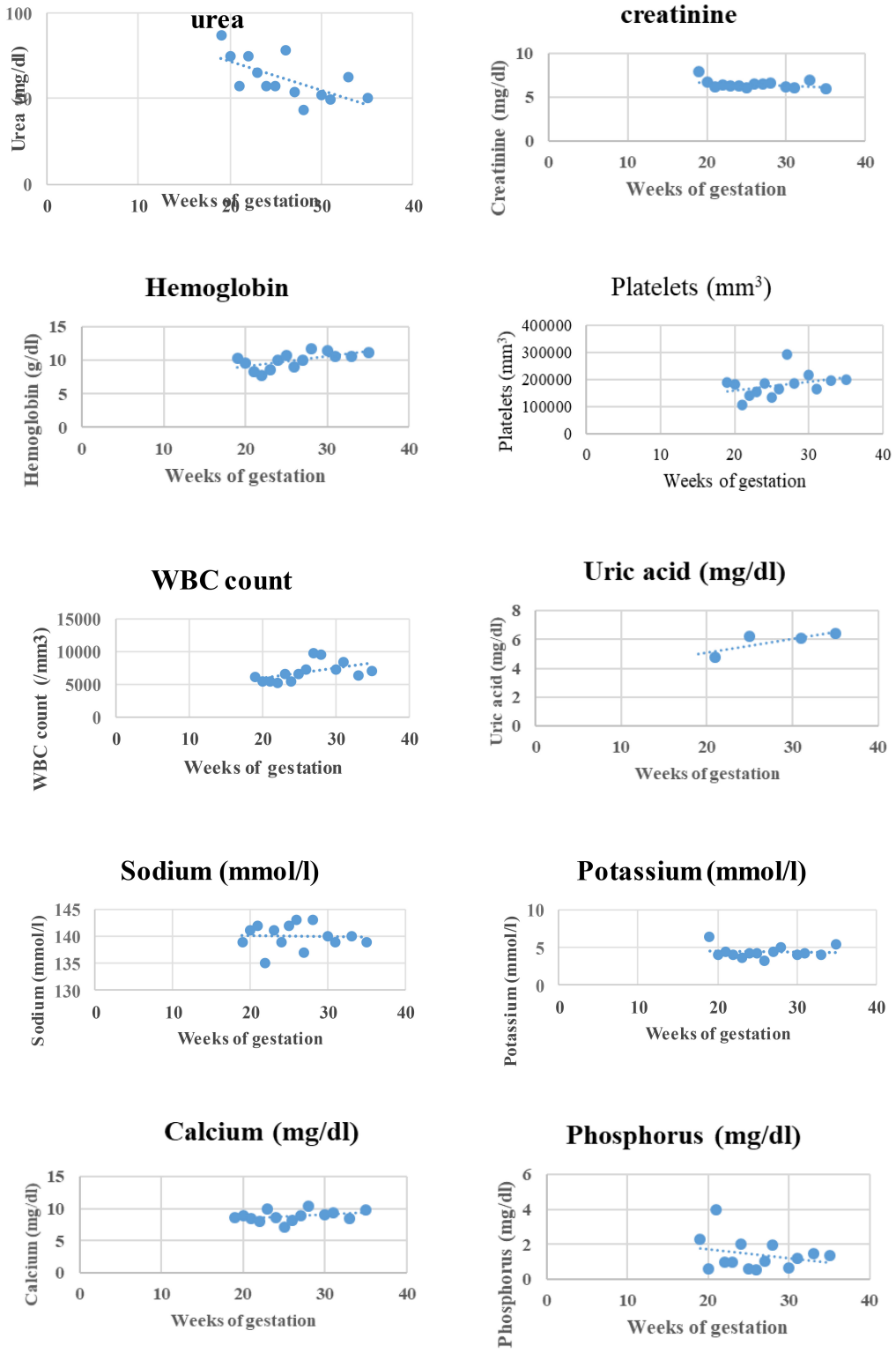

FIGURE 2
Evolution of weekly biochemical parameters with gestational age.

Discussion

This is the third report of a successful pregnancy in a woman on MHD in Cameroon, however, this is the first case in an anuric woman after 7 years on MHD undergoing twice weekly hemodialysis sessions.

In Cameroon, the actual incidence of conception during ESKD is unknown but a cumulative incidence of conception among ESKD patients of childbearing age on MHD of 7.14% in 11 years was reported (2). In the early reports in Cameroon, conception occurred within the first year of hemodialysis (2, 6). This case report, however occurred after 7 years on MHD. The rate of conception and successful

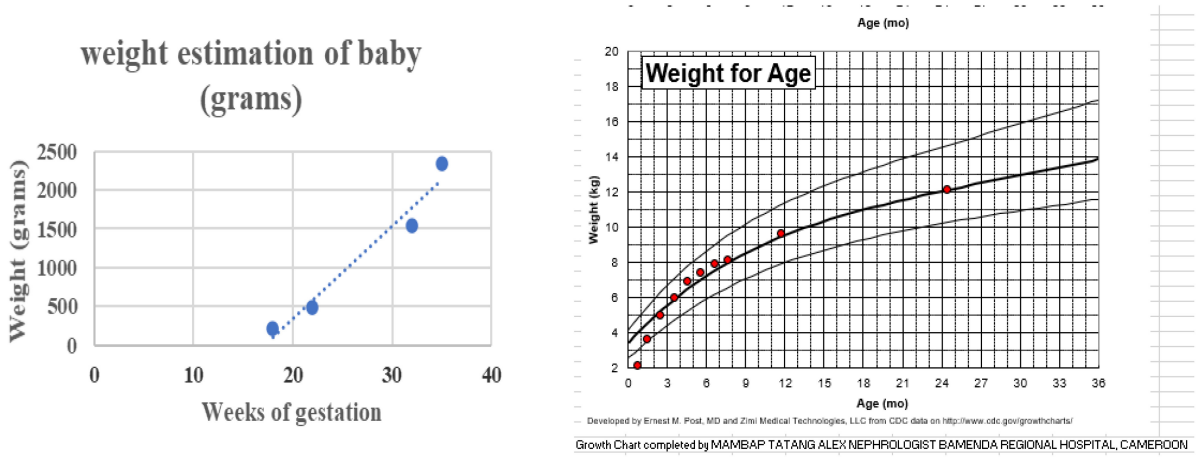

FIGURE 3
Intra-uterine and extra-uterine weight change of the child.

outcome of pregnancies on HD reduce with longer HD vintage of women (8). In addition, compared with previously reported cases in the country, our patient was anuric for many years. Most studies report more frequent conception and successful pregnancies when the patients have residual renal function (7, 8).

The diagnosis of pregnancy in our case was late (18 weeks of gestation) because her amenorrhea was not a new finding, and she had few suggestive symptoms. Only an increase in abdominal volume was the key, and ultrasound was the diagnostic tool used to confirm the pregnancy. A similar finding was observed in previous pregnancies in Cameroon with an average age of diagnosis of 15.8 ± 4.02 weeks (2). Indeed, in this population, ultrasound seems to be the only clear diagnostic tool compared with the β-HCG assay, whose level rises with a decrease in renal function (8).

We have achieved a successful pregnancy outcome up to 36 weeks and 4 days. The stabilization and maintenance of an optimal level of blood pressure control and increase in HD frequency and length of dialysis sessions were the factors that permitted us to prolong gestation and resulted in higher birth weight compared with previous reports cases. Most studies suggest that increasing dialysis time to more than 20 h per week during pregnancy results in a longer gestational period, a higher number of viable pregnancies, and a higher birth weight (5, 9). Indeed, this increase in dialysis time induces the reduction of plasmatic urea and uremic toxins, which favor a better maternal diet and better blood pressure control with good control of intra-vascular and extra-vascular fluid mass.

TABLE 3 Summary of work-up of the child at 4 years.

Work-up	Results
Serum urea	11.5 mg/dl
Serum creatinine	0.6 mg/dl
Serum sodium	144 mmol/L
Serum potassium	5.3 mmol/L
Serum chloride	106 mmol/L
Serum calcium	10.5 mmol/L
Hepatitis B surface antigen	Negative
Urinalysis	Areactive SG: 1,015 pH: 6.5
Renal ultrasound	Both kidneys are normal sizes (The right measuring—6.5 cm in length and the left 6.9 cm with parenchymal thickness of 1.4 cm) with normal corticomedullary differentiation with normal calyces, ureter, and bladder

The increase of hemodialysis frequency and length and success to maintain the pre-dialysis blood urea between 50 and 55 mg/dl permitted us to avoid polyhydramnios. The pathophysiology of excessive amniotic fluid production is unclear, with one of the suggested mechanisms being fetal solute diuresis, due to high concentrations of urea and other uremic toxins in the maternal blood. Many studies confirmed that the incidence of polyhydramnios decreases with the increase in total dialysis time and kept blood urea at a low level (7).

The number of antihypertensive drugs was increased through pregnancy to control blood pressure. In literature, high blood pressure has been reported in about 80% of patients, with 40% developing severe hypertension, which needs three or more drugs for control (3). The mechanism of hypertension, in this case, is probably multifactorial. It can be the result of pregnancy itself or the use of high-dose EPO.

During the follow-up, the patient received two pints of packed red blood cells despite the use of EPO. This same picture was noted by Giatras et al. who observed a drop in hematocrit even during human recombinant EPO-treated pregnancies and the persistence of the requirement for blood transfusion (7).

The pregnancy was ended by cesarean section because of multiple fetal risks by vaginal delivery (maternal–fetal virus transmission, tight nuchal cords, and intrauterine growth retardation).

Conclusion

This case adds to the growing body of evidence supporting improved pregnancy outcomes in Sub-Saharan African women undergoing hemodialysis, and it gives Cameroonian women of childbearing age on hemodialysis hope that they may be able to

consider a successful pregnancy. The importance of contraception for women on HD, even if they have amenorrhea, is also highlighted in this report. Finally, this report emphasizes that the successful outcome of pregnancy in women undergoing hemodialysis in Sub-Saharan Africa is dependent on the patient's ability to afford the high costs associated with this management, particularly in a setting without health coverage.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of details of her medical case.

Author contributions

AM, EB, and SL performed the follow-up of the patient. FS and KK did the follow-up of the child. AM, KK, SL, and GA wrote the manuscript. All the authors read and approved the final version for publication.

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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Case report: Applicability of breastfeeding the child of a patient with kidney failure with replacement therapy

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This case report highlights the benefit or harm of breastfeeding in a patient with Kidney Failure with Replacement Therapy (KFRT) undergoing program hemodialysis. This is a unique clinical case, as pregnancy and successful delivery are rare in this group of females. With a favorable outcome, the possibility of breastfeeding is especially relevant for doctors and the mother. The patient was a 31-year-old female who was diagnosed in 2017 with end-stage renal disease associated with chronic glomerulonephritis. Against the background of hemodialysis, pregnancy, accompanied by polyhydramnios, anemia, and secondary arterial hypertension, occurred in 2021. At 37 weeks, a healthy, full-term baby girl was born, and breastfeeding was started. In this study, we conducted a detailed analysis of toxic substances and immunologically significant proteins using high-tech analysis methods. In addition, we studied different portions of milk before and after hemodialysis at different time intervals. After a wide range of experiments, our study did not reveal an optimal time interval for breastfeeding a baby. Despite the decrease in the level of the major uremic toxins 4 h after the hemodialysis procedure, their level remained high. In addition, the content of nutrients did not reach acceptable limits and the immune status was characterized as pro-inflammatory. In our opinion, breastfeeding is not advisable for this group of patients since the concentration of nutrients is low, and the content of toxic substances exceeds the permissible limits. In this clinical case, the patient decided to stop breastfeeding one month after delivery due to insufficient breast milk and the inability to express it in a certain period of time.

KEYWORDS

case report, breastfeeding, immunology, Kidney Failure with Replacement Therapy (KFRT), biochemistry, molecular physics

Introduction

Motherhood with Kidney Failure with Replacement Therapy (KFRT) requires critical and comprehensive attention, starting with the possibility of pregnancy, its maintenance at high risks of miscarriage, to postpartum complications. Patients with KFRT are approximately 100 times less likely to have a live birth (1) than a female without kidney disease. Nevertheless, thanks to

the advances in medicine and the well-coordinated work of a council of physicians, the number of successful pregnancies in patients on hemodialysis has been growing in recent years.

From an evolutionary and nutritional perspective, exclusive breastfeeding during the first 6 months of life has been recognized as the gold standard of infant nutrition (2). The benefits and indispensability of breastfeeding for the harmonious development of the child have been confirmed by numerous studies (3–5). Milk promotes optimal growth of the child, including the establishment of circadian rhythms, the production of protective antibodies, and the formation of a healthy gut microbiome (6).

However, the benefits of milk have been well demonstrated for healthy mothers; little is known about how KFRT and hemodialysis procedures affect the quality and benefits of breast milk or whether maternal toxins and metabolites pass from the blood into milk.

Elevated levels of uremic toxins impair the normal functioning of various organ systems. In particular, the neurotoxic effect of water-soluble guanidine compounds, which include creatinine, was shown (7). In addition, uremic toxins disrupt endothelial functions causing structural damage, inflammation, and disruption of endothelium-dependent vasodilation (8, 9).

Uremic toxins affect both the innate and adaptive immune systems through multiple mechanisms, leading to systemic pathologies in humans. The accumulation of uremic molecules and cytokines activates the innate immune response, leading to a vicious cycle that stimulates the production of cytokines and ROS, which are known to increase the risk of cardiovascular disease and tissue damage (10). Moreover, uremic toxins have a pro-apoptotic and/or inhibitory effect on immune cells, contributing to an increased risk of infections (11, 12).

Uremic toxins can lead to diarrhea by disrupting the intestinal microflora. Hydrolysis of urea with the formation of a large amount of ammonia increases the intestinal pH, which leads to irritation of the intestinal mucosa and may have a negative effect on the growth of commensal bacteria that contribute to the maintenance of intestinal dysbacteriosis (13).

All of the above raises the question of the potential harm of breast milk, including it in the long term. Therefore, neonatologists and pediatricians face the important question of whether breastfeeding should be recommended to mothers on hemodialysis.

Case presentation

The patient was a 31-year-old female diagnosed in 2017 with end-stage renal disease associated with chronic glomerulonephritis. Family, genetic, and psychosocial history was not aggravated. She underwent a living-related kidney transplantation, but the transplant was removed due to chronic cellular humoral rejection. In 2021, she was transferred to renal replacement therapy using the program hemodialysis. In the same year, against the background of hemodialysis, she had a pregnancy accompanied by polyhydramnios, anemia, and secondary arterial hypertension. This was the second pregnancy of the female: the first (before KFRT) ended in a spontaneous miscarriage in the second trimester. The patient was offered a therapeutic abortion, but it was refused. During pregnancy, the regimen of renal replacement therapy was changed: the program hemodialysis procedure was carried out for 3 h 30 min 6 times a week. Dialysis regimen: hemodiafiltration; weekly dialysis time—20–24 h; vascular access—native arteriovenous fistula; blood flow rate—320 ml/min; the dialysate flow rate—500 ml/min; Fresenius FX 60 dialyzer. Hemostabilization during the procedure—enoxaparin sodium. To correct anemia, the dose of erythropoietin was increased from 4,000 to 6,000 IU/week. Iron (III) hydroxide sucrose complex dose increased from 100 to 200 mg per month (intravenously).

Biochemical and ultrasound screening at 19 weeks revealed congenital malformations in the fetus (pyelectasis and megaureter on both sides). At the 23rd week, hemostatic therapy was performed in labor due to the threat of premature delivery. A diet with sodium, phosphorus, and potassium restrictions, compliance with the water-drinking regime was recommended. Antihypertensive therapy: Methyldopa 250 mg × 2–3 times a day while controlling blood pressure. Iodine, folic acid, ascorbic acid, calcium preparations, vitamin D were prescribed. Therapy with gestagens (Utrogestan 200 mg × once a day) was carried up to the 34th week. At the 28th week, isthmic-cervical insufficiency was corrected with an obstetric pessary. Antibiotic therapy was conducted to prevent infectious complications (Cefazolini 1.0).

At the 37th week, a planned cesarean section was performed for delivery. A lower midline incision was performed in order to prevent trauma to the iliac regions for reinsertion of the renal graft. A live full-term girl, weighing 2,460 g and 47 cm tall, was retrieved. Apgar score was 8/9 points. The dynamics of renal function parameters during pregnancy and after delivery are shown in **Supplementary Table 1**. The mother's conscious decision was to start breastfeeding.

At the first stage of the study, we found that the composition of the breast milk of a patient on hemodialysis differed from that of healthy mothers in the control group in several aspects. Fresh portions of milk a month after birth were used to assess the level of milk's biochemical parameters, including the major uremic toxins (creatinine, urea).

In our study, we used urea (60 Da) and creatinine (113 Da) as the most representative low molecular weight uremic toxins that are widely used as surrogate markers for detecting kidney function in the clinic. Urea and creatinine are easy to measure with reliable and inexpensive assays in routine laboratory practice (14).

Since there are no reference values for most of the analytes we measured in milk, the milk of healthy females ($n = 5$) with a similar duration of breastfeeding, collected with informed voluntary consent, served as a control. When studying the level of biochemical parameters in milk samples, a significant increase in the content of uremic toxins, particularly creatinine and urea, in milk both before hemodialysis and after the procedure compared with control samples of healthy females was shown.

Since the female was highly motivated to breastfeed, it was of the utmost importance for the clinicians to assess the effect of the hemodialysis procedure on her breast milk over time and to find the optimal time to express the least dangerous portions of milk. For this purpose, samples of the patient's breast milk were collected for further research at different time intervals during the day: before the hemodialysis procedure; immediately after the hemodialysis; 4, 7, and 13 h after the end of the hemodialysis procedure. The experiments showed that the lowest content of creatinine and urea was observed not immediately after the hemodialysis procedure but 4 h after its completion, which could be explained by the redistribution of toxic substances from the tissues into the blood (**Figure 1**).

One of the advantages of breastfeeding is the stimulating effect of breast milk on the humoral development of immunity, which leads to a decrease in the incidence of illness in children. In this regard, we assessed the concentration of immunoglobulin IgA, sIgA, and IgM

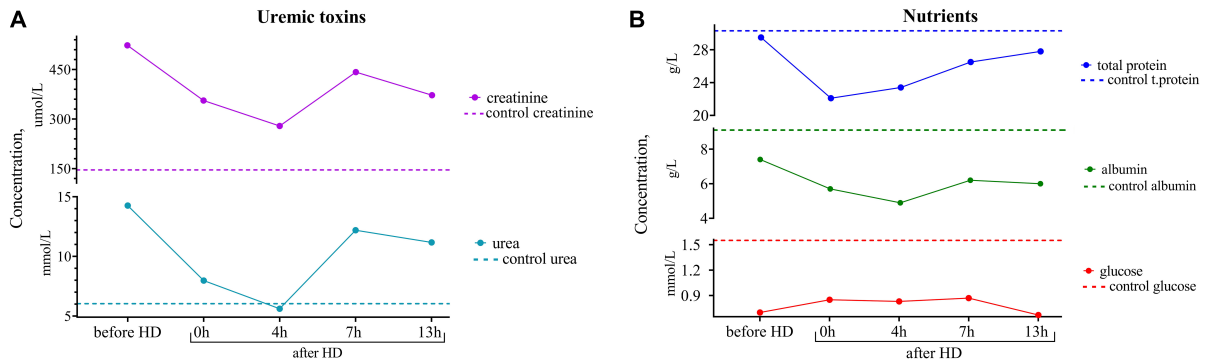

FIGURE 1
(A) Dynamics of uremic toxins (creatinine and urea) and **(B)** nutrients (total protein, albumin, and glucose) concentrations in the breast milk of the patient undergoing renal replacement therapy by program hemodialysis. The horizontal axis presents time relative to the hemodialysis procedure: before HD, immediately after HD (0 h), 4, 7, and 13 h after hemodialysis. The vertical axis shows the concentration of analytes. Dashed lines indicate the average concentration of each analyte in the control sample (breast milk of healthy females with the same lactation period).

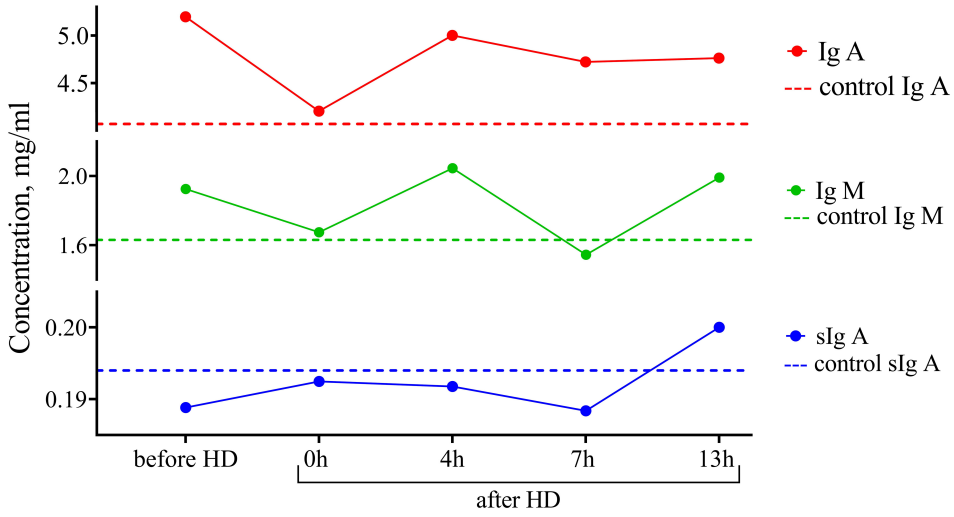

FIGURE 2
Dynamics of the concentration of immunoglobulins of IgA, IgM, and sIgA subclasses in the breast milk of the patient undergoing renal replacement therapy by program hemodialysis. The horizontal axis presents time relative to the hemodialysis procedure: before HD, immediately after HD (0 h), 4, 7, and 13 h after hemodialysis. The vertical axis shows the concentration of analytes. Dashed lines indicate the average concentration of each analyte in the control sample (breast milk of healthy females with the same lactation period).

subclasses in breast milk (Figure 2). The content of immunoglobulins did not differ from the control, and there were no significant peaks in the dynamics of concentrations before and after hemodialysis.

Breast milk is known to be the main source of cytokines, especially anti-inflammatory ones, for newborns, who are usually deficient in these proteins. Using multiplex cytokine analysis with the Luminex XMAP technology, we assessed a range of pro-inflammatory and anti-inflammatory cytokines in breast milk at different time points after hemodialysis. The results are presented in Figure 3. There was an increased level of pro-inflammatory cytokines in milk both before and after the hemodialysis procedure compared with the control. Pro-inflammatory cytokines, which, according to the literature data, also accumulate in uremia, belong to medium-molecular uremic toxins (15).

At the same time, there was a tendency for the level of pro-inflammatory cytokines to fall 7 h after the hemodialysis procedure. The level of the major anti-inflammatory cytokines (Il-4, Il-10) at all measurement points was lower than in the control samples.

For the most targeted study of milk composition, a series of experiments was carried out to investigate the molecular physical properties. Multi-angle dynamic light scattering (MADLS) was used to determine milk particle sizes, reflecting the diffusion properties of its constituent molecules. Based on the data on hydrodynamic diameter distributions, it can be concluded that low- (~70–200 nm), medium- (~400–500 nm), and high-molecular (500–1500 nm) compounds or aggregates were present in the milk samples of a patient with KFRT (Figure 4A). A study of milk samples using fluorescence spectroscopy showed that the patient's milk sample collected before hemodialysis had a higher fluorescent activity compared to control samples (Figure 4B). The fluorescence intensity after hemodialysis decreased by 10%, approaching the fluorescence of the control sample. After that, the fluorescence increased, returning to its original value after 7 h. At the same time, the fluorescence emission peak shifted from 329 nm immediately after hemodialysis to 327.5 nm 13 h after the end of the procedure. The second fluorescence peak (327, 229 nm) also behaved unusually. After hemodialysis,

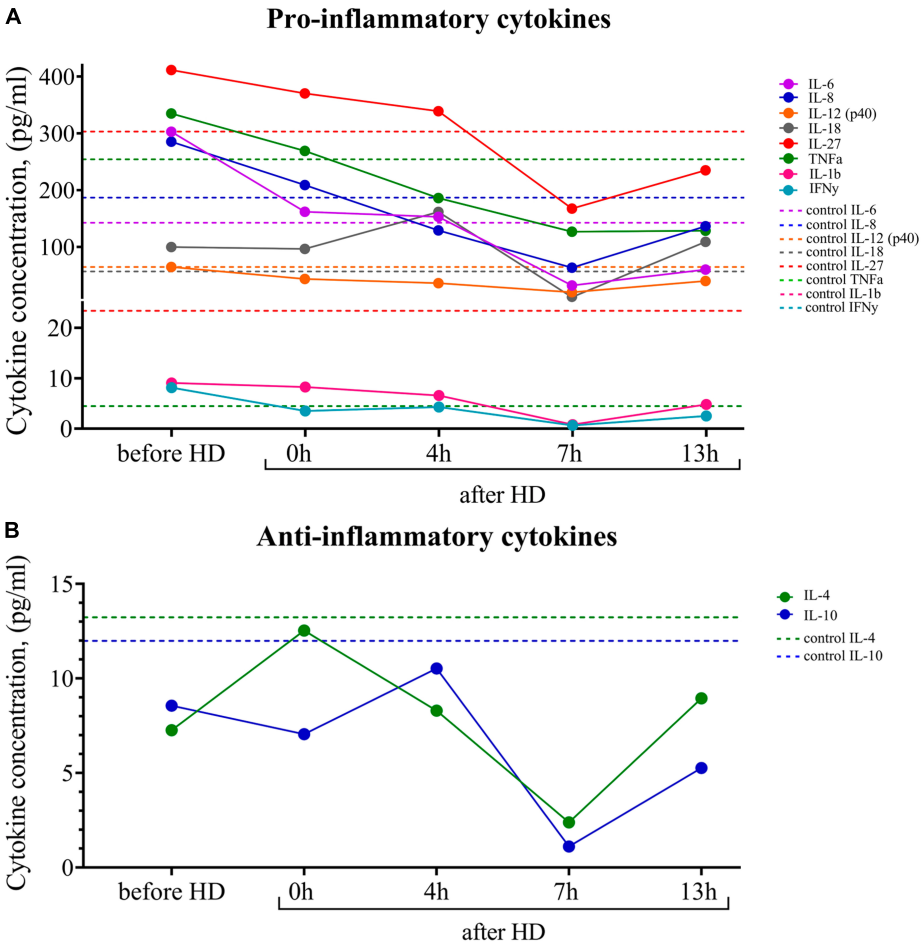

FIGURE 3
(A) Dynamics of pro-inflammatory and **(B)** anti-inflammatory cytokine concentrations in the breast milk of the patient undergoing renal replacement therapy by program hemodialysis. The horizontal axis presents time relative to the hemodialysis procedure: before HD, immediately after HD (0 h), 4, 7, and 13 h after hemodialysis. The vertical axis shows the concentration of analytes. Dashed lines indicate the average concentration of each analyte in the control sample (breast milk of healthy females with the same lactation period).

the intensity of the second peak decreased by 20%, and after 4 h, it was restored to its original values before hemodialysis. A slight shift in the emission maximum during fluorescence from 326 to 328 nm may indicate a different protein composition of the milk of a healthy participant and a sick patient. This is also evidenced by the absorption of proteins in the UV (absorption due to amino acids) and the visible region (absorption due to aggregates and micelles), where the control sample absorbed more than the patient's milk sample both before and after hemodialysis (the results are presented in **Supplementary Table 1**).

Discussion

Pregnancy, childbirth, and breastfeeding in KFRT are courageous steps that only some patients dare to take. Breast milk is undoubtedly the best source of nutrition for an infant and has health benefits for the mother. It ensures the proper development of the immune system, programming of endocrine and metabolic functions (5). Breastfeeding is recommended whenever possible, with or without supplementary feeding, depending on the baby's needs. However, the decision to breastfeed should be as balanced and deliberate as possible, taking into account the impact on the mother and child.

To the best of our knowledge, there are no clear guidelines for breastfeeding in chronic kidney disease (CKD) and KFRT. The only generally accepted recommendations are to counsel patients in the early stages of CKD and before kidney transplantation regarding pregnancy complications. A single case of breastfeeding in patients with CKD has been described in the literature. In their study, Balzer et al. (6) showed that breastfeeding may be a viable option for newborns from mothers on dialysis, as the composition of their breast milk has more similarities than differences with that of healthy mothers. The authors report that breastfeeding after a dialysis session is preferable to breastfeeding before dialysis. However, in this study, the conclusion about the applicability of breastfeeding is based primarily on immunoglobulin levels, which were found to be the same in healthy females and patients on hemodialysis.

We disagree with the statement above since the risk to the child of a mother with KFRT who is breastfed cannot be excluded. The decision to stop breastfeeding should be made based on an assessment of the benefits of breastfeeding for the baby and the benefits of therapy for the mother. Breastfeeding in KFRT is challenging, not only due to the impact of the hemodialysis procedure

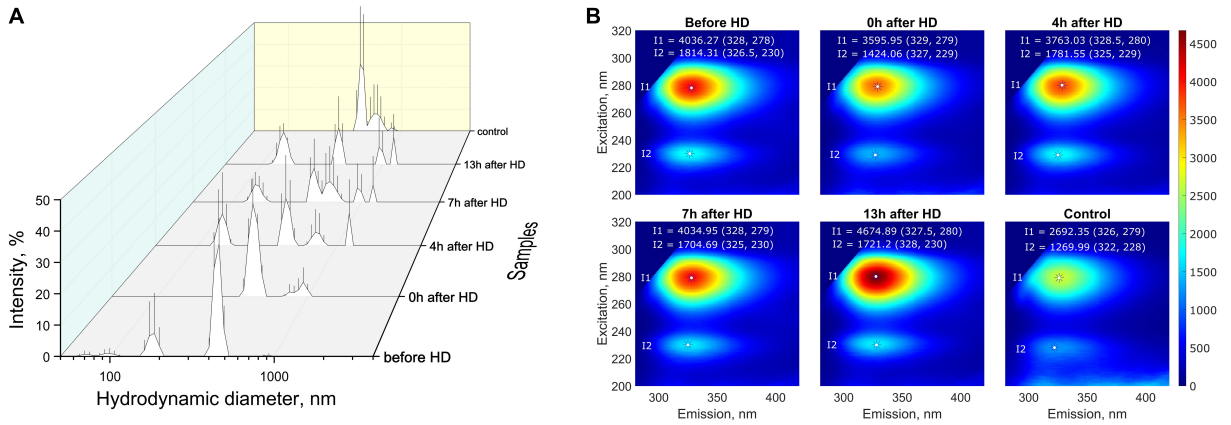

FIGURE 4
(A) Distribution (intensity weighted) of hydrodynamic particle diameters obtained by MADLS in milk samples from the patient with KFRT at various time intervals (before HD, immediately after HD (0 h), 4, 7, and 13 h after HD) and in control samples (milk of healthy females with the same lactation period); **(B)** fluorescence spectra of breast milk samples. Milk samples from a patient with KFRT have higher fluorescent activity compared with control samples.

but also due to the adverse effects of drugs on infants and lactation itself. Experts also raise concerns about the mother's ability to feed her baby, given her clinical condition after a complicated, high-risk pregnancy (4).

In our study, we conducted a detailed analysis of toxic substances and immunologically relevant proteins using high-tech analysis methods. The advantage of the approach is the study of milk portions before and after the hemodialysis procedure at different time intervals. As a result, after a wide range of experiments, our study did not reveal an optimal time interval for breastfeeding a child.

Despite the decrease in the level of major uremic toxins 4 hours after the hemodialysis procedure, their level remained high. It is known that high concentrations of urea can cause protein denaturation (16), which has an extremely bad effect on the composition of milk, blocks digestive enzymes, and changes the conformation of immunoglobulins (17). In addition, due to its osmotic properties, the urea solution can provoke diarrhea, which is very unfavorable for a baby in the first months of life.

Low and medium molecular weight compounds identified by MADLS are most likely associated with protein micelles (18), while high molecular weight compounds are associated with fat aggregates (19). However, such a division is rather arbitrary in the presence of lipoprotein micelles in a wide range of sizes (20). The presence of low molecular weight compounds that are not present in control samples may also be associated with the presence of toxic substances, such as certain lipoprotein modifications, advanced glycation end products (AGEs), and lipooxidation in KFRT patient milk, which are of comparable size (21). The changes in the fluorescence of patient's samples after hemodialysis are of particular interest. These changes indicate that hemodialysis leads to significant changes in the protein content in the milk of a patient with KFRT.

Some experts believe that it is necessary to encourage and remove barriers to breastfeeding, where appropriate, for mothers with KFRT on dialysis or after transplantation. The authors refer to the fact that "breast milk is the perfect food." However, it is important to remember that any nutritional deficiencies that exist during pregnancy will eventually be carried over through lactation (22). In our study, the content of nutrients, especially proteins, did not reach acceptable limits.

Since cytokines are known to activate and maintain the body's immune response and reduce the risk of chronic diseases, we believe it is important to focus on their ratios in breast milk. Abnormal cytokine production may have negative health consequences and can contribute to the development of food allergies, jaundice, and immune disorders in later life (23–25). In the given case study, we note the pro-inflammatory status of the milk of a female with KFRT, which can negatively affect the child.

A limitation of the given study is the lack of clinical data on the condition of the child after birth.

Conclusion

To sum up, the results obtained raise the question of the need for further research on the applicability of breastfeeding in patients with KFRT undergoing program hemodialysis. In our opinion, breastfeeding is not advisable for this group of patients since the concentration of nutrients is low, and the content of toxic substances exceeds the permissible limits. In this clinical case, the patient decided to stop breastfeeding a month after delivery due to insufficient breast milk and the inability to express it in a certain period of time.

Data availability statement

The original contributions presented in this 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.

Author contributions

EK, SG, and MV contributed to conception and design of the study. EK and NL organized clinical data collection. EK and AF wrote the first draft of the manuscript. AF prepared the figures. EN, RM, and SG wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

NL was employed by Branch FESFARM NN.

The remaining 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1098324/full#supplementary-material

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Typical course of cystinuria leading to untypical complications in pregnancy: A case report and review of literature

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Cystinuria is a rare genetic disorder inherited by an autosomal recessive pattern which affects the transmembrane transporter for the base amino acid cystine. It has a general prevalence of 1 in 7000 with demographic variations. Patients with cystinuria have excessive urinary excretion of cystine, which can lead to the formation of stones. Up to 70% of patients will develop chronic kidney disease that can progress even to end-stage renal disease. Symptoms usually start in the first two decades of life with a typical presentation consisting of flank pain and renal colic, usually accompanied by urinary tract infection and deterioration of kidney function. Men are typically affected twice as often as women and have a more severe clinical course. Diagnosis is made by spectrophotometric analysis of the stones that are collected after spontaneous expulsion or medical intervention. Genetic testing is not mandatory but is recommended in uncertain cases or as a part of genetic counseling. Treatment consists of diet modification, alkalization of urine, and thiol-based therapies if other measures fail to prevent stone formation. In pregnancy, cystinuria with the formation of cystine stones represents a therapeutic challenge and requires a multidisciplinary approach consisting of an uro-nephrology team and a gynecologist. We present the case of a 34-year-old woman with cystinuria on whom the diagnosis was made by analysis of the expulsed stone. While her previous pregnancies were without complications, her third pregnancy was accompanied by frequent urinary tract infections, acute worsening of kidney function, and urological interventions during pregnancy due to the formation of new stones. Despite the complicated course, the pregnancy was successfully carried to term with the delivery of a healthy female child.

KEYWORDS

cystinuria, pregnancy, case report, chronic kidney disease, multidisciplinary approach

Introduction

Cystinuria is a rare genetic disorder that affects the transmembrane transporter for the base amino acid cystine leading to excessive excretion of cysteine in urine that induces stone formation. Cystine transporter $b^{0,+}$ is located in the proximal tubule. Its heterodimer is combined of two subunits—rBAT and $b^{0,+}$ AT connected with a disulfide bridge (1). Solute carrier protein 7

(*SLC7A9*) located on chromosome 19 encodes subunit $b^{0,+}$ AT, while solute carrier protein 3 (*SLC3A1*) located on chromosome 2 encodes for rBAT. Currently, there are more than 200 mutations connected with *SLC3A1* and more than 100 mutations associated with *SLC7A9*, but according to some authors, up to 5% of patients have cystinuria without known mutation (2). Transepithelial transporter is also responsible for the transportation of ornithine, lysine, and arginine (COLA) (3).

According to the International Cystinuria Foundation, cystinuria can be divided into three types. In Type I, both parents are heterozygotes, and it is usually caused by a mutation in *SLC3A1*. In non-Type I cystinuria, patients have non-type alleles from both parents, and it is caused by a mutation in *SLC7A9*. Patients with non-Type I cystinuria usually have a variable degree of cystine excretion, and they are not prone to cystine formation. The third type is the mixed type with both Type I and Type II alleles. Due to the lack of genotype–phenotype correlation, it has been advised to define cystinuria according to genetics to Type A, where mutations are found in both *SLC3A1* alleles; Type B, where mutations are found in both *SLC7A9* alleles; and putative type aB, where one mutation is found in each gene (4) and which has a prevalence of 1 in 7000, but there are ethnic and demographic variations (5).

Clinical symptoms usually start around the first two decades of life. Patients with cystinuria have an excessive excretion of cystine in the urine, usually above 400 mg/day (1). Male patients have a more severe clinical presentation with the earlier occurrence and more stones (2, 6). In general, around three-quarters of patients will present with bilateral stones (2, 6, 7). CKD is an important aspect of cystinuria because up to 70% of patients will develop CKD, which can then lead to ESRD (2, 8). Diagnosis is usually made using ultrasound or CT scan, by analyzing the stones that are excreted in the urine, and by the presence of high levels of cystine excretion (1). Genetic testing is not mandatory, but it is recommended as a helpful tool for genetic counseling (9). Treatment is based on dietary advice with adequate hydration, alkalization of urine, and thiol-based therapy, including D-penicillamine and tiopronin, as well as a urological intervention, which includes retrograde ureteroscopy and/or PCNL (1).

Symptomatic nephrolithiasis can complicate 1 in 3300 pregnancies (10), and the incidence of urolithiasis in pregnancy can vary from 1:188 to 1:4600 (11, 12). Having a pregnant patient with cystinuria is challenging for both the nephrologist and the obstetrician. While the impact of cystinuria on pregnancy has not been well studied, it is well known that management is challenging due to regular stone formation and difficult imaging during pregnancy. Therefore, we present an illustrative case of a pregnant patient with cystinuria followed by a multidisciplinary team of urologists, nephrologists, and gynecologists, concluding with a full-term delivery of a healthy child.

Case description

We present a case of a female patient who was first treated in our hospital at the age of 34 years after an episode of renal colic. Analysis of the expulsed stone showed a cysteine structure. She had a positive family history of chronic kidney disease (CKD) with her brother developing end-stage kidney disease, and she was receiving renal replacement therapy at the age of 28 years. Her medical history revealed an episode of urinary tract infection (UTI) and passing of the urinary stone at the age of 23 years. At the time, she received antibiotic therapy and no further workup was performed. Subsequently, the patient was without any symptoms and had two pregnancies. The first pregnancy had an unremarkable course but her second pregnancy was terminated with an urgent cesarean section in the 39th week with delivery of a healthy child.

At the time of presentation in our hospital, her kidney function was mildly reduced (eGFR 86 mL/min/1.73m^2) without albuminuria or proteinuria. Ultrasound showed a normal left kidney without signs of lithiasis, while the right kidney had a slightly reduced parenchyma of 10 mm and 3rd degree hydronephrosis. CT scan confirmed hydronephrosis of the right kidney with an impacted stone in the pyelon. Dynamic scintigraphy showed significant functional damage (25%) of the right kidney. After spontaneous expulsion, the stone was sent for analysis that revealed cysteine formations. The case was discussed with the urological team, and in May 2021, a right percutaneous nephrostomy was performed due to obstruction with atrophy of the parenchyma. Dynamic scintigraphy after the procedure showed no improvement in the right kidney function. She was hospitalized in August 2021 for right pyelotomy with ureteral stenting (double J stent) and removal of nephrostomy. One month later she presented with a UTI and worsening kidney function with eGFR of 23 mL/min/1.73m^2. CT scan showed multiple stones of the left kidney in the lower and middle calyces and cast stones in the lower columns and pyelon. The right kidney was hypotrophic with lobulated contour, signs of post-inflammation changes, and multiple mineral stones along with the previously placed double J stent (Figures 1, 2). Treatment with broad-spectrum antibiotics and hydration was commenced. The right double J stent was replaced and another double J stent was placed in the left kidney. Following treatment, the kidney function started to improve along with a fall in inflammatory markers.

A few weeks later, she was again hospitalized for left percutaneous nephrolithotomy (PCNL), replacement of left double J stent, and left percutaneous nephrostomy. Both double J stents were subsequently removed. At that time, the patient was already pregnant but was not aware of it.

Due to high-risk pregnancy, a multidisciplinary team was assembled, consisting of a nephrologist, urologist, and obstetrician,

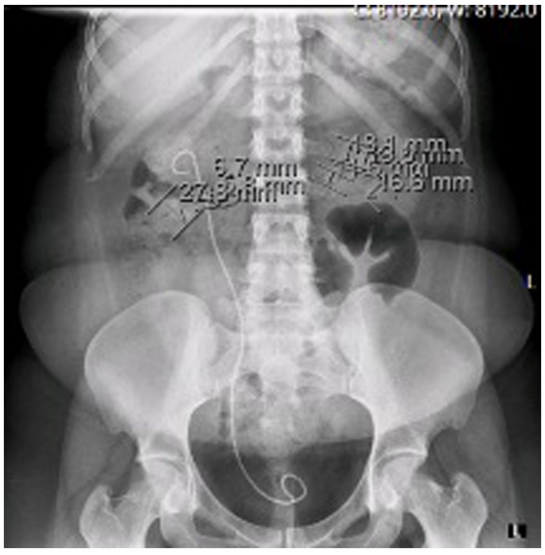

FIGURE 1
KUB at the time of acute kidney injury.

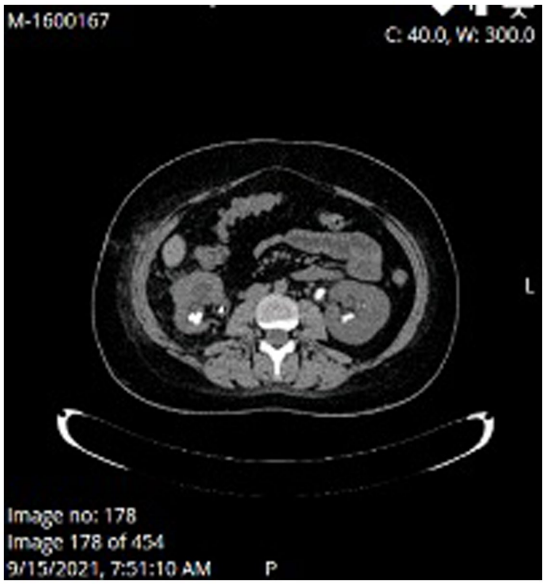

FIGURE 2
MSCT at the time of acute kidney injury.

with scheduled regular monthly check-ups. Her pregnancy was complicated by recurrent UTIs despite prophylaxis with oral fosfomycin and potassium citrate therapy for the alkalinization of urine. Her kidney function remained within normal range and without proteinuria until the 25th week of gestation. At that time, she developed again left renal colic with obstructive nephropathy (grade II hydronephrosis) and acute worsening of kidney function (eGFR 36 mL/min/1,73 m^2). Under ultrasound guidance, a double J stent was placed again in the left ureter and her kidney function quickly improved to remain normal thereafter, with only slight proteinuria of 0.5–0.6 gram per daily urine (g/d).

In the 38th week of pregnancy, she underwent elective cesarean section delivering a healthy female child with a normal birth weight. The patient was re-evaluated after 3 months. Her kidney function returned to normal (eGFR 82 mL/min/1,73 m^2) with proteinuria of 0.41 g/d and albuminuria of 0.147 g/d. Cystine values were 111 mmol/mol creatinine (normal level up to 17 mmol/mol creatinine). The treatment with tiopronin was discussed with the patient but, for the time being, the patient opted not to take any medication during lactation.

Discussion

There are very little data in the literature regarding the management and outcome of pregnancy in patients with cystinuria. Management of urolithiasis in pregnancy has its specific set of problems due to the potential harm that ionizing radiation can have on the developing fetus. The primary diagnostic tool used in a pregnant woman who presents with a clinical picture indicative of ureterolithiasis is an ultrasound of the kidney and bladder. CT scan is contraindicated because of the aforementioned reasons and MR urography is usually unavailable (13).

Due to the physiological stasis of the urine in the kidneys during pregnancy which occurs usually after the 11th week, ultrasound alone does not have sufficient specificity and sensitivity to diagnose ureteral stone in the clinical setting of a potential nephrocolic (14). However, the incidence of urolithiasis does not differ compared to women who are not pregnant (13, 15).

The initial workup of a pregnant female with cystinuria consists of clinical examination and blood workup to exclude uroinfection, while at the same time, analgesic therapy is given to alleviate pain (mostly acetaminophen) (13). Nonsteroidal anti-inflammatory medications should not be given because of adverse consequences for the developing fetus, especially in the first and third trimesters (14). In the case of uroinfection, drainage of the infected and obstructed kidney is necessary. The double J stent and the nephrostomy tube have the same therapeutic effect. Due to the rapid development of encrustations, there is a need for regular replacements of either the double J stent or the nephrostomy tube until delivery (13, 14). In some tertiary centers, ureteroscopy is a therapeutic option, especially in the central trimester, and when done by an experienced endourologist (16). Fortunately, in more than 80% of cases, conservative treatment leads to spontaneous expulsion of the stone without the need for further interventions (17).

Pregnant women with cystinuria who are hospitalized for nephrolithiasis have a higher risk of preterm delivery and pyelonephritis (18). Gregory et al. (18) published an article describing 46 pregnancies in patients with cystinuria who were treated with a high fluid intake alone or in combination with D-penicillamine. Of 46 pregnancies, 41 resulted in live births of normal children, four had spontaneous abortions, and one was terminated due to concerns for the mother's health. These authors reported that in 18 patients, new calculi appeared. Renal colic appeared in seven patients and two patients passed stones. In our patient, stones were not excreted in urine during pregnancy, but she had several renal colic attacks which presented with acute worsening of kidney function, and this led to hospitalization, antibiotic treatment, and urological interventions. Although hypertension is a common complication of cystinuria (1), our patient had normal blood pressure during the entire pregnancy.

Thiol-based drugs in pregnancy have been used according to literature and published case reports. FDA is advising against the use of tiopronin in pregnancy (19), but available data do not reveal significant drug-associated risk for adverse maternal or fetal outcomes, miscarriage, or major birth defects. Tiopronin and metabolites are not excreted in human milk nor were found in the serum of children whose mothers were taking tiopronin during lactation (20). Nevertheless, it is not recommended during lactation due to other adverse effects such as nephrotic syndrome. Furthermore, tiopronin can induce a significant reduction in prolactin and suppress lactation (20). D-penicillamine has FDA pregnancy categorization D, which means that there is evidence of human fetal risk, but in some cases, potential benefits can outweigh the risk (21).

Shee and Pais Jr. published a case report of a pregnant patient who presented with flank pain and moderate hydroureter seen on ultrasound, treated with nephrostomy tube placement during pregnancy, and after full-term cesarean section, the patient underwent PCNL that revealed cystine stone as the culprit (22). As opposed to Shee and Pais Jr. (22), although presenting with similar symptoms, our patient already had complications and urological interventions during early pregnancy, as well as later. Unlike the majority of patients with cystinuria, of which around 70% have CKD, our patient had stable kidney function at the time of diagnosis, despite the hypofunction of one kidney. The brother of our patient was already treated with renal

replacement therapy at the age of 28 years and a major concern, in this case, was the possibility of deterioration of kidney function during pregnancy. Despite a complicated course of pregnancy, her kidney function deteriorated only as a consequence of obstruction with quick improvement after urological intervention.

It is important to emphasize the importance of a multidisciplinary approach in these specific cases. In our case, the patient was regularly seen by a nephrologist, urologist, and obstetrician and was monitored for potential complications, and treated adequately when they occurred. The patient had a successful pregnancy in the end, but her pregnancy course was complicated, so it is important to advise female patients with cystinuria of available methods of contraception, especially if they already had children, to avoid possible negative outcomes.

Conclusion – patient perspective

Reports on pregnancy with cystinuria are scarce in the literature. Pregnancy leads to several physiological changes, including changes in the urine content of metabolites. Ultrasound is a readily available tool and should be used as a standard of care in all pregnancies which will aid in the early diagnosis of urolithiasis. If ultrasound had been done in the first two pregnancies, our patient would probably have been diagnosed with cystinuria earlier and very probably hypofunction of the right kidney could have been prevented. This case shows that even patients with complex medical problems and complicated disease courses during pregnancy can still have a successful perinatal outcome.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the patient to publish this case report, including all data and images.

Author contributions

IE has analysed data and literature about the article and made design and conception of this article. MM has equally contributed in revision of this manuscript with advices about urological clinical course. E-GV has equally contributed in revision of the manuscript and gave advices about gyaenocological clinical course. FPM has equally contributed in revision of the manuscript and gave perspective and advices from nephrologist perspective. LL has equally contributed in revision of the manuscript and gave advices from paediatrician perspective. JB has equally contributed in this article and gave advices for nephrologist perspective. VI has equally contributed in revision of this manuscript and helped in critical revision. All of the authors have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to Frontiers in Medicine. All authors had equally participated in final approval of the article, administrative, technical or logistical support.

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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Case report: Sevelamer-associated colitis—a cause of pseudotumor formation with colon perforation and life-threatening bleeding

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Chronic kidney disease (CKD) is a very common chronic non-communicable disease. Phosphate and calcium metabolism disorders are one of the most common features of CKD. Sevelamer carbonate is the most widely used non-calcium phosphate binder. Gastrointestinal (GI) injury associated with sevelamer use is a documented adverse effect but is underrecognized as a cause of gastrointestinal symptoms in patients with CKD. We report a case of a 74-year-old woman taking low-dose sevelamer with serious gastrointestinal adverse effects causing colon rupture and severe gastrointestinal bleeding.

KEYWORDS

gastrointestinal lesion, gastrointestinal bleeding, colon rupture, chronic kidney disease, sevelamer carbonate, case report

1. Introduction

Sevelamer is an anion exchange resin used to lower hyperphosphatemia in CKD. Originally approved in 1998 as sevelamer hydrochloride, it has been largely replaced by sevelamer carbonate. Although both medications have similar efficacy, sevelamer carbonate has a lower risk of metabolic acidosis (1). Treatment of hyperphosphatemia is crucial in CKD patients, given its well-known association with vascular and endothelial damage, as well as increased mortality (2–4). Sevelamer is a calcium-free phosphate binder, thus avoiding the positive calcium balance induced by calcium-based binders, which is associated with increased mortality in CKD patients (5). It has also been suggested that sevelamer has beneficial pleiotropic effects (6). Sevelamer is a non-absorbable resin able to bind the phosphate in the gastrointestinal tract. Although side effects reported in patients receiving sevelamer include nausea, diarrhea, vomiting, dyspepsia, abdominal pain, flatulence, and constipation, there is little research to determine the mechanism of gastrointestinal symptoms (7). Sevelamer can also cause gastrointestinal tract motility disorders, which is mostly attributable to sevelamer hydrochloride (7).

Sevelamer-associated gastrointestinal injury presents a diagnostic challenge and is probably underrecognized cause of gastrointestinal symptoms in patients with CKD. Sevelamer has been shown to have mucosal deposits throughout the gastrointestinal

tract with great variability in associated symptoms. However, the most common clinical presentation of sevelamer-induced GI lesions is GI bleeding, followed by acute abdomen and GI discomfort (8). Diabetics seem to be more prone to develop sevelamer-associated GI lesions (8). Mucosal ulceration including wall perforation and post-inflammatory stricture formation are among the serious complications (10–16). There is also one report describing sevelamer induce colitis presenting as pseudotumor (11). Some patients with sevelamer-induced GI lesions had previous GI diseases (dyspepsia, peptic ulcer, diabetic gastroparesis, ulcerative colitis), GI infection caused by Clostridium difficile, or major abdominal surgery (8–16). Concomitant anticoagulant and/or antiplatelet therapy may also have influenced the clinical presentation (8–16). The average daily dose of sevelamer taken by the patients with GI lesions is 4.8 g (range 0.8–9.6 g), but the association between the sevelamer dosage and the severity of GI lesions was not clearly established (8). There is also no clear association between the form of the drug (powder or tablet) or anion content (carbonate or hydrochloride) and the quantity or severity of GI lesions (8). The summary of previous reports of gastrointestinal lesions induced by sevelamer is presented in Table 1.

Notable mucosal abnormalities found in patients with sevelamer-associated GI lesions include chronic mucosal damage, acute inflammation, inflammatory polyps, extensive ulceration, ischemia, and necrosis (9). Histological features of sevelamer crystals include irregularly arranged "fish-scale" crystals found within the GI mucosa with different colors during *in vitro* and *in vivo* studies (9). Patients with sevelamer deposits in the GI tract can also be asymptomatic (8).

As mentioned above, there is little information documenting serious gastrointestinal bleeding or colon rupture with sevelamer as a cause. Here we describe a case of sevelamer-induced various life-threatening gastrointestinal complications, namely bleeding, and pseudotumor, in a single patient on a low dose of sevelamer.

2. Case report

A 74-year-old woman with several comorbidities (arterial hypertension, diabetes mellitus, valvular heart disease, and chronic kidney disease) was admitted to the hospital due to lower gastrointestinal bleeding resulting in hemodynamic instability and shock.

The initial event of lower gastrointestinal bleeding was documented during the hospitalization 7 months earlier. At that point, the patient presented with rectorrhagia and worsening renal function. A multi-slice computed tomography scan scan revealed a thickened wall of the ascending colon and hepatic flexure with no other significant pathology. Lower endoscopy showed inflamed and friable mucosa of the entire circumference of the transverse colon, splenic flexure, and part of descending colon with normal rectal mucosa. Taking into account the typical endoscopic appearance, the patient was diagnosed with ischemic colitis. Her diabetes was well controlled with dietary measures. She had high C-reactive protein levels and was treated with antibiotics including ciprofloxacin and metronidazole which resulted in complete clinical and laboratory normalization (Table 2). Stool cultures were negative. Due to unspecific inflammation in the colon mesalazine was added (3 g/day). At discharge, the treatment with sevelamer carbonate was induced (1.6 g /day) due to worsening of the kidney function and hyperphosphatemia. Importantly, the patient was not taking sodium polystyrene sulfonate or any other cation exchange resin. Mesalazine therapy was stopped after 3 months since the patient had no GI symptoms.

TABLE 1 Summary of previous reports of GI lesions induced by sevelamer.

Author/Year of publication	Number of cases	Age (years)/Gender	Preexisting GI disease	Sevelamer dosage (grams/day)	Sevelamer crystals in mucosa
Swanson et al. (9)	Case 1 Case 2 Case 3 Case 4 Case 5 Case 6 Case 7	59/f 68/m 38/m 49/f 53/m 66/m 81/m	No No Yes No No Yes No	9.6 4.8 4.8 7.2 2.4 N/A 4.8	Yes Yes Yes Yes Yes Yes Yes
Chintamaneni et al. (14)	Case 1	61/ f	No	7.2	Yes
Okwara et al. (11)	Case 1	79/m	No	N/A	Yes
Kim et al. (13)	Case 1	17/f	Yes	2.4	Yes
Tieu et al. (12)	Case 1	74/f	Yes	4.8	Yes
Yamaguchi et al. (10)	Case 1	66/m	No	4.5	Yes
Yuste et al. (8)	Case 1 Case 2 Case 3	51/f 53/m 76/f	No Yes Yes	8.8 9 0.8	Yes Yes Yes
Uy et al. (16)	Case 1	33/m	Yes	7.2	Yes
Cockrell et al. (15)	Case 1	65/f	N/A	N/A	Yes

GI-gastrointestinal, f-female, m-male, N/A-not applicable.

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TABLE 2 The laboratory results and clinical course of the patient.

	January 2022 Hospitalization due to rectorrhagia	October 2022 Hospitalization due to rectorrhagia	October 2022 Hospitalization due to severe rectorrhagia, hypotension
	Therapy (daily dosage): propranolol 40 mg Furosemide 40 mg Amlodipine 5 mg Perindopril 8 mg Vitamin D supplement Ciprofloxacin 250 mg metronidazole 1200 mg Mesalazine 3 g (3 months course) Sevelamer carbonate 1600mg (beginning of treatment- at discharge)	Therapy (daily dosage): propranolol 40 mg Furosemide 40 mg Vitamin D supplement Sevelamer carbonate 1,600 mg Meropenem 500 mg i.v. Mesalazine 3 g (reintroduced) Prednisone 40 mg	Therapy (daily dosage): propranolol 40 mg Furosemide 40 mg, vitamin D Sevelamer carbonate 1,600 mg (discontinued) Meropenem 500 mg i.v. Mesalazine 3 g Prednisone 40 mg (discontinued) Fluid replacement Blood transfusions Ciprofloxacin 400 mg Metronizdol 1500 mg Total colectomy, formation of terminal ileostomy
Hemoglobin (RR 119–157 g/l)	92	106	70
Hematocrit (RR 35-47 %)	28	33	22
Leucocytes (RR 3.4–9.7x10E9/l)	7.7	17.8	32.8
Creatinine (49–90 μmol/l)	466	290	207
GFR (RR> 60 ml/min/1.73m2)	<15	<15	20
Potassium (RR 3.7–5.0 mmol/l)	5.2	5.6	4.2
Calcium (RR 2.14–2.53 mmol/l)	1.93	2.09	N/A
Phosphorus (RR 0.79–1.42 mmol/l)	2.04	1.00	N/A
C-reactive protein (RR <5 mg/l)	74.9–17.5–12.1	120.9–34.9	11
Stool cultures	negative	negative	N/A
Endoscopy	Multiple lesions in descendent and transverse colon	Multiple ulcerations in transverse colon	The lumen of colon filled with fresh blood; it was not possible to visualize the bleeding site
Pathohistological finding	Non-specific inflammation Ischemic colitis	N/A	Severe mucosal injury, acute inflammation within the bowel wall, sevelamer crystal within the luminal debris

RR, reference range, N/A, not applicable.

The patient was readmitted after 7 months and presented with diarrhea and abdominal pain. Her laboratory results showed again significantly increased inflammatory markers, but with negative stool cultures. Her kidney function was stable (Table 2). Endoscopy was performed and revealed a large ulceration in the transverse colon encompassing the whole circumference of the colon (Figure 1). A multi-slice computed tomography scan showed a significantly thickened wall of the cecum, ascending and transversal colon.

The patient was treated empirically with meropenem alongside other supportive treatments. Due to the presence of inflammatory changes in the colon, inflammatory bowel disease was suspected and, prednisone was started with rapid clinical and laboratory improvement. The patient was discharged after 10 days of hospitalization with normal bowel movements and no other symptoms. Two days after discharge, she was readmitted due to severe lower gastrointestinal bleeding with hemorrhagic shock. Despite the intensive treatment measures the patient remained unstable, and given the impossibility of definitive endoscopic hemostasis with hemodynamic instability patient was referred to urgent surgery.

Intraoperatively, the colon was described as malignantly altered, with the tumor-changed central part of the transverse colon, and the retained perforation. The total colectomy and terminal ileostomy were performed. The histopathological finding of the colon described severe mucosal injury with acute inflammation and visible characteristic "fish-scale" crystals of sevelamer within the luminal debris, accompanied by acute inflammation and focal necrosis of the bowel wall, with no signs of dysplasia or malignant alteration (Figures 2A, B). The

conclusion of these findings was that the necrosis of the colonic wall was caused by sevelamer, and the drug was discontinued. Postsurgical recovery was complicated by an episode of cardiac decompensation which resolved with optimized diuretic treatment. The patient was discharged after 8 days of hospitalization in stable clinical condition.

3. Discussion

Sevelamer is an anion-exchange resin designed for the treatment of hyperphosphatemia in patients with chronic renal disease. Its structure is made of a non-absorbed hydrogel with ammonia on the hydrochloride or the carbonate. Due to the acidic content of the stomach, the polymer dissociates from its anion and consequently is available to bind phosphate within the intestine (17). Sevelamer also causes dehydration in the intestinal tract, resulting in the formation of hard stool (7).

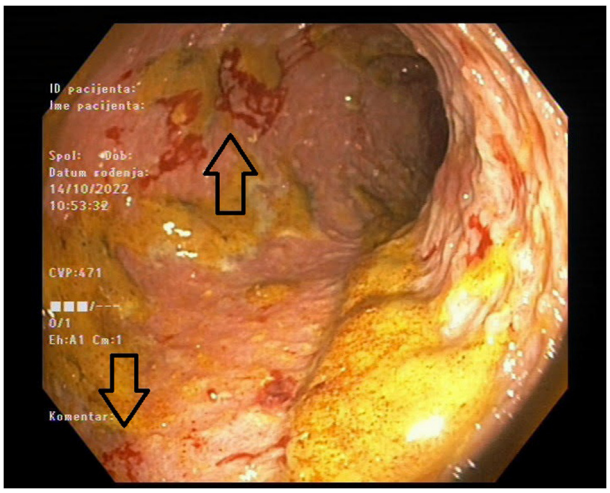

FIGURE 1
Colon endoscopy showing diffusely inflamed and ulcerated mucosa of transverse colon.

Despite the side effects reported in patients receiving sevelamer, e.g., nausea, diarrhea, vomiting, dyspepsia, abdominal pain, flatulence, and constipation, there is little research to determine the direct mechanism of sevelamer on the gastrointestinal tract (18–20). Post-marketing data show rare cases of ileus and intestinal obstruction, attributable mainly to sevelamer hydrochloride, but the frequency of severe intestinal adverse effects is unknown (7). The direct effect of hard stool and constipation following sevelamer administration may trigger perforation, but given the lack of investigation the potential cause remains unclear. Moreover, in patients undergoing hemodialysis, hypotension episodes and hypovolemia may cause mesenteric ischemia and intestinal necrosis, making the mucosa more vulnerable to other causes of injury (9, 10). Swanson et al. described the histopathology of sevelamer crystals in the GI tract, and their association with mucosal abnormalities which can be found in the esophagus, small bowel, and colon (9).

It has been reported that patients on hemodialysis have a high risk of colonic perforation even without sevelamer administration, and there were no significant changes in the incidence of bowel perforation after the approval of sevelamer (21, 22).

In our case, the patient had the serious adverse effects of sevelamer therapy presenting with life-threatening GI hemorrhage. Although our patient was diagnosed with ischemic colitis, she responded well to mesalazine therapy and had no GI symptoms.The sevelamer was induced after the first hospitalization when her GI symptoms resolved. Thus, we cannot conclude with certainty that our patient had an underlying GI disease, contrary to theother reports in the literature (8–16). On the other hand, our patient is diabetic, which makes her more prone to sevelamer-induced GI lesions (8). Our patient was treated with a relatively low dose of sevelamer (1.6 g/day), and the duration of therapy was only seven months. However, previous reports did not establish the association between the sevelamer dosage and the severity of GI lesions, which occurred also in patients taking 800 mg sevelamer daily (8). Moreover, our patient showed characteristic histopathological findings of sevelamer crystals in lesion biopsies and direct deposition of sevelamer crystals in areas of ulceration and pseudotumor formation was found. In conclusion, we believe that sevelamer use is the most likely etiology of pseudotumor

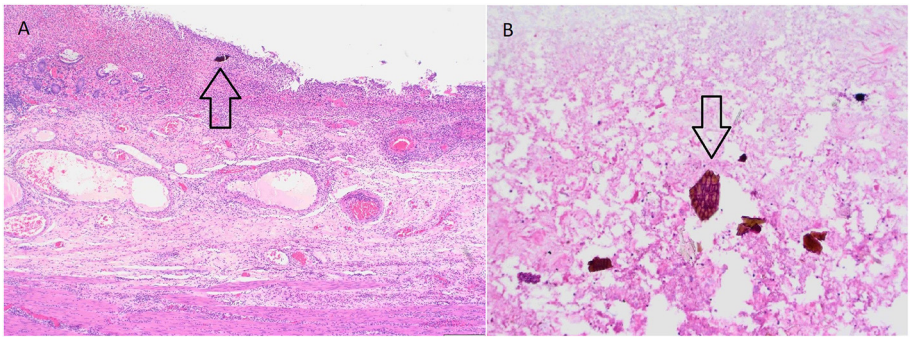

FIGURE 2
(A) Severe mucosal injury with acute inflammation within the bowel wall. Note the sevelamer crystal within the luminal debris. (H&E, 40x). **(B)** Sevelamer crystal within the luminal debris—characteristic fish scale appearance with orange and pinkish hue (H&E, 200x).

formation and restrained rupture of the transverse colon in our patient. Sevelamer-induced GI lesions should always be considered in CKD patients treated with sevelamer who present with GI symptoms, especially lower GI bleeding, regardless of the sevelamer dosage. Sevelamer therapy should be prescribed with caution in patients with a history of major abdominal surgery, chronic GI disease, and diabetes given the high risk of serious GI complications in this patient population.

4. Patient perspective

Our patient was hospitalized twice in a short period of time due to abdominal pain and bloody stools. Her appetite was poor and she was feeling ill, but responded well to treatment. A few days after being discharged, she was again hospitalized due to bloody stools and abdominal pain. She felt very weak. After the surgery, she had breathing difficulties, which resolved after therapy. She was discharged from the hospital and is currently in-home care.

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.

Author contributions

MF, MJ, MB, DG, and IR: substantial contribution to the conception of the work, interpretation of findings, drafting the work, and final approval of the report. ZM: analysis of kidney biopsy material, interpretation of findings, critical revising of data for the work, and final approval of the report. EI: substantial contribution to the conception of the work, interpretation of data, critical revising of the work, and final approval of the report. BJ, IV, and ZK: interpretation of data, critical revising of the work, and final approval of the report. All authors contributed to the article and approved the submitted version.

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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Minimal change disease associated with thyroid cancer: a case report

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A patient complaining of edema of the face and lower extremities was admitted to the nephrology department for nephrotic syndrome. Renal biopsy revealed findings of minimal change disease (MCD). Thyroid ultrasound showed a hypoechoic 16 × 13 mm nodule in the right lobe, suspicious of malignancy. Later, total thyroidectomy confirmed the diagnosis of papillary thyroid carcinoma (PTC). After surgery, MCD remitted rapidly and completely, strongly suggesting the diagnosis of MCD secondary to PTC. We report here the first adult case of the paraneoplastic finding of MCD secondary to PTC. Additionally, we discuss the possible role of the *BRAF* gene in the pathophysiology of PTC-associated MCD in this case and highlight the importance of tumor screening.

KEYWORDS

minimal change disease, secondary nephropathy, paraneoplastic glomerulopathy, thyroid cancer, *BRAF*

Introduction

Minimal change disease (MCD) is a major cause of nephrotic syndrome (NS), characterized by severe proteinuria and a good response to steroid treatment. MCD can be triggered by drugs, infections, allergies, tumors, and lymphoproliferative disorders. To date, there is limited clinical experience with tumor-related MCD. We herein report the first adult case of MCD secondary to papillary thyroid carcinoma (PTC) and discuss the possible role of the *BRAF* gene in the pathogenesis of PTC-associated MCD in this case.

Case report

A 38-year-old woman was admitted to our nephrology department with facial and lower extremities edema and a weight gain of 4.5 kg for 3 days. Her medical history was remarkable for angina pectoris and chronic hepatitis B. She denied allergy, recent infection, COVID vaccination, occupational exposure to heavy metals, or family history of renal diseases. Physical examination revealed bilateral pretibial edema and a 15 × 10 mm, hard, painless, irregular nodule on the right side of her neck.

Laboratory tests (Supplementary Table 1) showed hypoalbuminemia (serum albumin 19.9 g/L) with hyperlipidemia (total cholesterol 8.52 mmol/L, low-density lipoprotein 6.45 mmol/L). Complete blood count, C-reactive protein and renal function were unremarkable.

HbsAg, HbeAb and HbcAb were positive, but HBV viral load was low (HBV DNA <500 IU/ml). Test results for HCV, HIV, and autoimmune antibodies were negative. Serum and urine protein immunofixation electrophoresis revealed no monoclonal proteins. Serum total thyroxine (T4) levels were slightly decreased (35.4 ng/ml), while triiodothyronine (T3), free T4, free T3, and thyroid-stimulating hormone levels were within the normal range. Macroalbuminuria was noted, with a urinary protein-creatinine ratio (UPCR) of 16.26 g/g and a protein excretion rate of 8.6 g/d. Ultrasonography revealed a 16 × 13 mm hypoechoic nodule in the right thyroid lobe with irregular shape and ill-defined margin. Color Doppler flow imaging showed abundant blood flow to the lesion, highly suggestive of thyroid malignancy (Figure 1). An enlarged lymph node (22 × 5 mm) was also noted in the right neck.

We performed a renal biopsy and an ultrasound-guided fine-needle aspiration (FNA) biopsy for the thyroid nodule. The specimen obtained by FNA suggested thyroid papillary carcinoma. Renal biopsy specimens on light microscopy showed no evident alterations in the glomeruli, tubulointerstitium or vessels. Immunofluorescence microscopy was negative for immune complexes but revealed weak deposits of IgM in the mesangium and focal staining for reabsorbed albumin particles in the tubules. Electron microscopy exhibited extensive podocyte injury, as evidenced by diffuse foot processes effacement, cytoplasmic vacuoles, and microvillous transformation (Figures 2A–H). Therefore, the patient was diagnosed with MCD and suspected thyroid papillary carcinoma.

Considering the presence of a malignant thyroid nodule, corticosteroids and other immunosuppressive therapies were deferred. Before the planned thyroidectomy, perindopril, an angiotensin receptor blocker (ARB), was used to decrease proteinuria. However, the patient discontinued perindopril after surgery. After a total thyroidectomy with a recurrent laryngeal nerve exploration, postoperative pathology confirmed the diagnosis of PTC (Figures 3A, B) with 6 level VI metastatic lymph nodes. The tumor cells were immunopositive for the BRAF (V-raf murine sarcoma viral oncogene homolog B1) protein (Roche Diagnostics) (Figures 3C, D). The surgical team ordered a *BRAF* mutation analysis using a quantitative fluorescent PCR with a human *BRAF V600E* mutation detection kit (Amoy Diagnostics, 1799T>A), which detected the *BRAF V600E* mutation. Surprisingly, proteinuria and serum albumin gradually normalized after surgery. At 6 months postoperatively, the patient achieved complete remission of MCD [proteinuria <0.3 g/d or UPCR <300 mg/g, serum albumin >3.5 g/dl according to the 2021 KDIGO guideline (1)], and no relapse occurred during a follow-up period of up to 30 months (Figure 4). The patient was satisfied with her treatment process and the clinical recovery. The case was finally diagnosed as PTC-associated MCD.

Discussion

To our knowledge, this is the first reported adult case of MCD secondary to PTC. Although approximately 50% to 60% of untreated MCD spontaneously remit over 2 to 3 years (1), in our case, the patient diagnosed with MCD was found to have PTC. Moreover, the patient achieved remission of MCD soon after tumor excision, strongly suggesting a link between MCD and PTC.

Paraneoplastic glomerulopathy is a condition of glomerular injury induced by products of tumor cells such as hormones, growth factors, cytokines, and tumor antigens (2). Compared with solid cancer-associated membranous nephropathy (MN) and Hodgkin lymphoma-associated MCD, the pathogenesis of solid cancer-associated MCD is less clear. In solid cancers, paraneoplastic MCD has been observed in lung cancer, colorectal cancer, renal cell carcinoma, and thymoma and less frequently in pancreatic, bladder, prostate, breast, and ovarian cancers (3, 4). In thyroid cancer, PTC has been associated with MN (5) and membranoproliferative glomerulonephritis (MPGN) (6). Liu et al. reported a case of minimal-change NS complicated with thyroid carcinoma in a pediatric case (7). However, it had a different clinical course

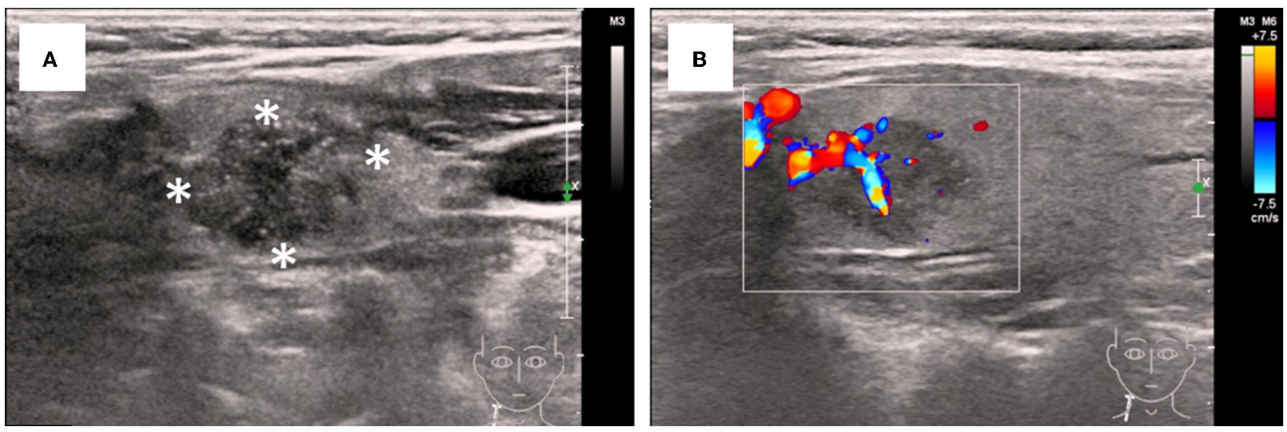

FIGURE 1
Ultrasonographic features of the thyroid nodular. **(A)** Irregular and ill-defined solid nodule with hypoisoechogenicity and microcalcifications (asterisks). **(B)** Increased vascular flow insides and around the nodular on color Doppler sonography.

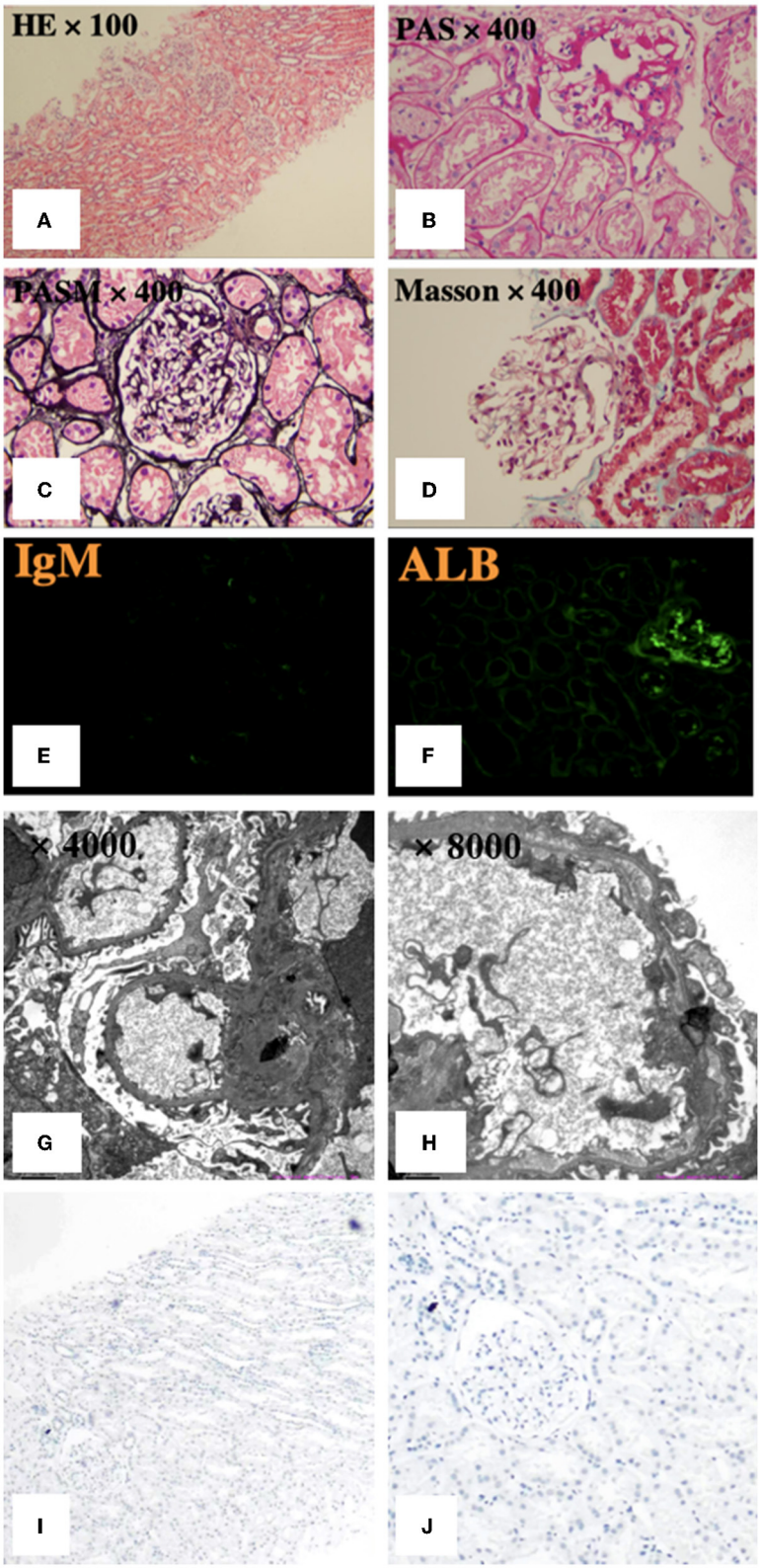

FIGURE 2
Pathological features of renal biopsy. **(A–D)** Light microscopy showed no apparent glomerular, tubulointerstitial or vascular alterations. **(E, F)** Immunofluorescence revealed weak deposits of IgM in the mesangium and focal staining for reabsorbed albumin particles in the tubules. **(G, H)** Electron microscopy exhibited extensive foot processes effacement, with no segmental sclerosis or electron-dense deposits, normal mesangial cellularity and matrix, and normal glomerular basement membrane thickness. PASM: periodic acid-silver methenamine, PAS: periodic acid-Schiff. **(I, J)** Immunohistochemistry staining for BRAF was negative.

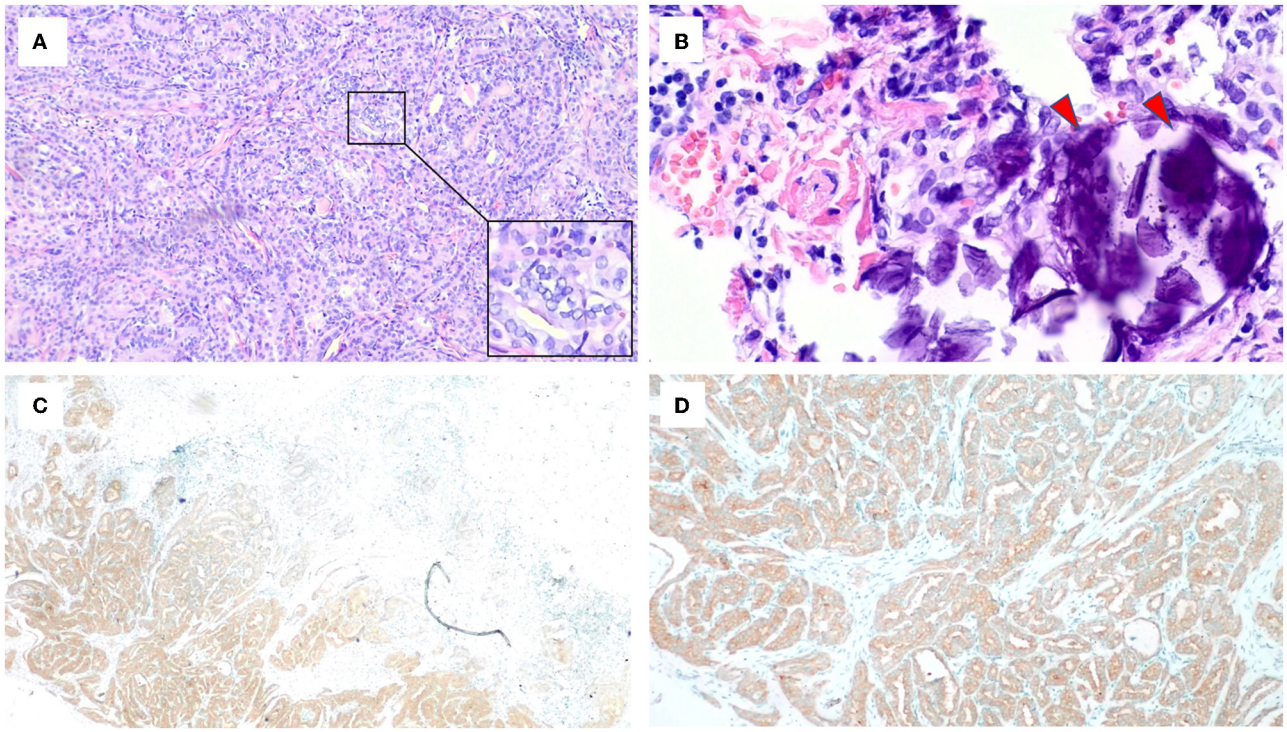

FIGURE 3
Microscopic appearance of papillary thyroid carcinoma. **(A)** Pathologic features reveal papillae lined by cuboidal to columnar cells with predominant nuclear changes. A magnification box on the right shows ground-glass nuclei with thick nuclear membranes, giving rise to what has been described as Orphan Annie Eye nuclei. Nuclear grooves are also noticeable (HE, ×10). **(B)** The presence of psammoma bodies shown by red arrows (HE, ×40). **(C, D)** Immunohistochemistry staining for BRAF was positive.

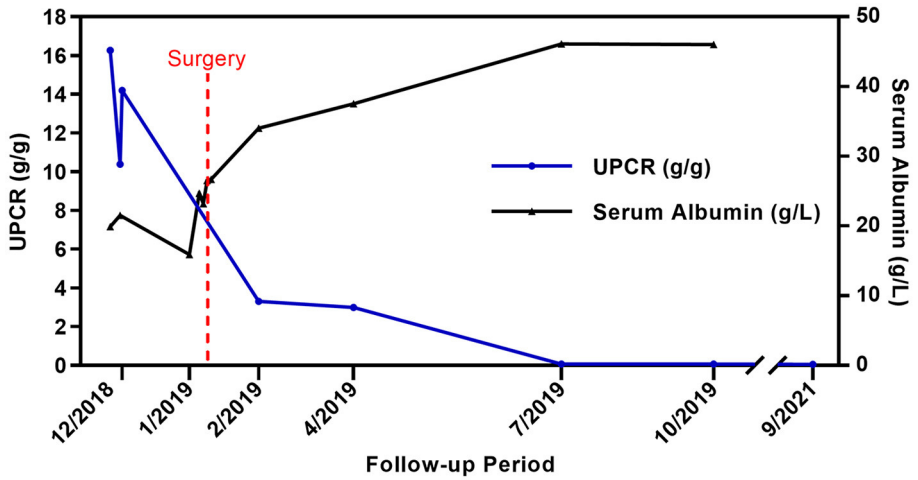

FIGURE 4
Clinical course of the patient. UPCR(blue line) and serum albumin (black line) changes before and after total thyroidectomy. Both UPCR and serum albumin normalized 6 months after the surgery (There was no spot urine or 24-h urine sample test performed in January 2019).

compared to our own. The child with MCD was found to have co-existing thyroid cancer and his condition did not improve after surgery; instead, he had multiple recurrences of NS. Fortunately, the child responded well to steroid treatment. In contrast, our patient achieved remission of MCD soon after tumor excision, strongly supporting the link between MCD and PTC in our case.

Interestingly, there is a strong correlation between renal manifestation and thyroid disorder. Physiologically, thyroid

hormones are essential for renal development and growth, while the kidney plays an important role in the metabolism and elimination of these hormones (8). When thyroid dysfunction occurs, there can be remarkable changes in glomerular and tubular functions, as demonstrated by the association between hypothyroidism /hyperthyroidism and nephropathy, tubulointerstitial nephritis. Likewise, renal disease can affect thyroid function, for instance, a higher prevalence of hypothyroidism has been observed in chronic kidney disease (CKD) (9). Furthermore, a reciprocal association between thyroid and renal cancers has been reported, suggesting that shared genetic and environmental risk factors may be at play (10).

In PTC, 40–45% of patients have a *BRAF* mutation, which is associated with an advanced stage and poorer prognosis. *BRAF* is a proto-oncogene that encodes the BRAF protein, a key component of the mitogen-activated protein kinase (MAPK) pathway. This pathway, more specifically the RAS-RAF-MEK-ERK pathway, regulates cell growth, proliferation, and apoptosis, and its alteration is one of the major contributors to tumorigenesis. Of the reported *BRAF* mutations, 98–99% are *V600E* mutations, which arise from the substitution of valine by glutamate at amino acid 600, and it is the most common mechanism of MAPK signaling activation in PTC (11).

In murine NS model, gene enrichment analysis in podocytes with foot processes effacement revealed upregulation of the BRAF/MAPK signaling genes (*RAF1*, *MAPK1*, *BRAF* as the leading genes), suggesting a podocyte-specific BRAF/MAPK signaling pathway (12). Analysis of a large gene database of human kidney diseases showed that the *BRAF* gene expression was elevated in several kidney diseases associated with podocyte damage, such as focal segmental glomerular sclerosis, lupus nephritis and MCD, and correlated with the severity of proteinuria (12). Moreover, the *BRAF V600E* inhibitor GDC-0879 has been shown to rescue podocyte foot processes effacement and promote podocyte survival *in vivo* and *in vitro* (13). However, there are also studies demonstrating that podocytes are protected when the MAPK pathway is activated (14), and podocytes are damaged when the *BRAF* gene is inhibited (15). Although the specific role of the *BRAF* gene in podocyte pathology remains controversial, these studies suggest that the abnormal expression of *BRAF* is implicated in podocyte dysfunction.

The relationship between the *BRAF* expression in tumor cells of PTC and podocytes is unclear. A common trigger, possibly molecular signals such as cytokines and microRNA released by tumor cells or microenvironment cells that affect the *BRAF* expression in these two distinct cell types, needs further investigation. Further study of the BRAF/MAPK pathway in podocytes before and after tumor removal might help to identify the upstream factors. In addition, there is dysregulation of T cells in both PTC and MCD (16–18), especially abnormal Th2 and related signaling pathways. Notably, the *BRAF* mutation in PTC is usually associated with the induction of immune tolerance and evasion (19, 20). Focusing on T cells and their signaling pathways by analyzing peripheral T helper cell subsets, cytokine levels, and Treg function may provide new insights.

Due to the close physiological and pathological relationships between the thyroid and the kidney, and reports of podocyte dysfunction caused by *BRAF* mutation, we explored the co-occurring gene events of thyroid and kidney in the patient. We performed immunohistochemistry staining (Roche Diagnostics) for BRAF in kidney tissues, which was immuno-negative (Figures 2I, J). There was no evidence of BRAF abnormality in the podocytes in our case, while the thyroid tumors was BRAF immuno-positive. Given the full recovery of podocyte dysfunction after tumor removal, there may be no intrinsic abnormalities in podocytes, and the podocyte dysfunction was related to PTC. Therefore, secondary MCD was considered for diagnosis.

In summary, we present here a rare adult case of PTC-associated MCD. The patient was successfully treated with thyroidectomy, which cured both PTC and MCD. Further studies are needed to elucidate the underlying mechanism of paraneoplastic MCD. From this case, we learn that individualized cancer screening in newly diagnosed nephropathy is reasonable in view of the possible, albeit rare, malignancy-associated nephropathy.

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 human participants were reviewed and approved by Ethical Committees of Shenzhen Second People's Hospital. The patients/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

XC wrote the first draft of the manuscript. YW and XZ contributed to the revisions of the manuscript. XC, QW, and XZ contributed to conception and design of the study. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1132259/full#supplementary-material

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Case report: A case of renal arcuate vein thrombosis successfully treated with direct oral anticoagulants

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A rare case of a 35 years old woman presented with renal arcuate vein thrombosis (RAVT) and acute kidney injury (AKI) following upper respiratory tract symptoms and toxic substance ingestion. Histopathological evaluation of the patient's kidney tissue indicated a rare venous thrombosis in the renal arcuate veins. Anticoagulation with Apixaban, a direct oral anticoagulant (DOAC), was commenced, and the patient's symptoms resolved during the hospital stay. Hitherto, a limited number of studies have shown the concurrent presentation of RAVT and overt AKI in patients following ingestion of nephrotoxic agents. Further studies are necessary to elucidate the etiology, clinical presentation, and treatment of RAVT. We suggest that Apixaban be studied as a suitable alternative to conventionally used anti-coagulants such as Warfarin in patients who lack access to optimal health care facilities.

KEYWORDS

renal arcuate vein thrombosis, direct oral anticoagulants, acute kidney injury, thromboembolism, Apixaban

Background

Thromboembolic events in the renal veins are rare and underdiagnosed status that can cause acute kidney injury (AKI) with life-threatening related conditions (1).

Due to the possible asymptomatic emergence and spontaneous resolution in some cases, renal vein thromboses (RVT) are often challenging to diagnose and be discovered incidentally by imaging studies (2–4). Therefore, the exact prevalence of RVT may be underestimated in the general population. However, special populations, such as renal transplant patients, present a prevalence rate of 0.1 to 6% (2, 3). Epidemiological studies on other disease groups, such as those afflicted with nephrotic syndrome and membranous nephropathy, have also shown a 5 to 60% prevalence rate (5, 6).

The etiology of RVT is no different from other forms of venous thrombosis and must be evaluated in the context of Virchow's triad (7). While states of dehydration are one of the most prevalent causes of RVT development in neonates, and RVT most commonly occurs secondary to nephrotic syndrome and renal transplantation in children (4), the etiology of RVT differs in adults. Glomerular pathologies such as nephrotic syndrome, hyper-coagulability, membranous glomerulonephritis, and non-glomerular entities such as neoplasia, rheumatologic

disorders, prior abdominal surgeries, trauma, and oral contraceptive use are known to play a role in RVT development in adults (8).

The most common clinical features of RVT that should be considered include flank pain, gross hematuria, nausea/vomiting, asterixis, and subsequent anemia (9).

An established cause of acute kidney failure is venous thrombosis of the extrarenal veins. While intrarenal venous thrombosis isolated from renal biopsies has not been widely reported; however, renal vein thrombosis may result from thromboembolic events occurring in the renal arcuate veins and cause overt AKI. Etiologic factors that cause this condition are not well understood, and they also happen without predisposing conditions such as nephrotic syndrome (10).

It is essential to treat the underlying precipitant, protect renal function, and prevent complications in RVT. To prevent thrombus progression and emboli, anticoagulation is recommended. Typically, unfractionated Heparin or low-molecular-weight heparin is initiated, followed by Warfarin for 6–12 months or until the underlying nephrotic disease is resolved. There are several indications for thrombectomy and/or thrombolysis in acute RVT, including bilateral RVT, treatment failure while on anticoagulation, thrombosis of the transplanted kidney, and thrombus extension into the inferior vena cava (IVC). It has been shown that fibrinolysis improves renal function and has a low risk of bleeding in the absence of contraindications (11, 12).

Although anticoagulants such as Heparin and Warfarin have been used to treat RVT (13), the effect of direct oral anticoagulants (DOACs) remains to be elucidated. Three patients with RVT treated with direct oral anticoagulants (DOACs) were included in the study conducted by Janczak et al. (14) regarding the use of the DOACs in unusual site VTE. A further four published case reports evaluate Rivaroxaban (15, 16), Apixaban (17), and Edoxaban (18) in patients with RVT with promising clinical outcomes.

Herein we demonstrate a rare case of RAVT, which presented with overt AKI and was treated successfully using Apixaban, a member of the DOACs family.

Case presentation

A 35 years old woman presented at the emergency department with a three-week history of dull abdominal pain, nausea/vomiting, urinary urgency, and urinary frequency from 2 days after using an Iranian herbal medicine compound for mild upper respiratory symptoms. It was noted that her spouse was positive for COVID-19, 10 days before her gastrointestinal and genitourinary symptoms emerged, and she had also developed mild myalgia and cough concurrent with her husband. On admission, the patient did not appear toxic, had no upper respiratory symptoms, but experienced unremitting abdominal pain. Physical examination was unremarkable except for a high blood pressure of 170/90.

Her medical history was significant for controlled asthma and gastroesophageal reflux disease (GERD), for which she took Salbutamol and Pantoprazole, respectively. There were no indications of alcohol drinking and using illicit substances.

Initial laboratory data showed a white blood cell count of $11.1 \times 10^3/\mu L$; the hemoglobin level was 10.1 g/dL. Her blood urea nitrogen (BUN) and serum creatinine (Cr) levels were 36 mg/dL and 8.53 mg/dL, respectively (Table 1). Hematuria (+1 Hb) was confirmed by urinalysis. However, viral markers, COVID-19 RT-PCR, blood cultures, and pregnancy tests were all negative. High levels of inflammatory markers such as ESR, CRP, and LDH were reported. Furthermore, the 24-h urinalysis did not indicate nephrotic range proteinuria (150 mg/dL in 24 h).

TABLE 1 Laboratory data of the studied case on 1st day, 7th day, and discharge time.

Blood tests	Initial data (on the 1st day, admission time)	Pre-dialysis data (on the 7th day, biopsy time)	Discharge data
Hb	10.1	11.3	11.6
WBC	$11.1 \times 10^3/\mu L$	$10.8 \times 10^3/\mu L$	$10.2 \times 10^3/\mu L$
Platelets	$232 \times 10^3/\mu L$	$240 \times 10^3/\mu L$	$228 \times 10^3/\mu L$
BUN	36 mg/dL	29 mg/dL	22 mg/dL
Cr	8.53 mg/dL	2.92 mg/dL	1.70 mg/dL
Na^+	138	140	142
K^+	4.9	4.5	4.1
Coombs test direct indirect	Negative	–	–

Ultrasonographic imaging of the urinary system showed normal size in both kidneys with increased parenchymal echo. A few tiny stones were seen in both kidneys, up to 6 mm in the mid-pole of the left kidney and 3 mm in the mid-pole of the right kidney. Minimal urinary stasis was also seen in the left renal pelvis, with no evidence of hydronephrosis. Color Doppler sonography of both renal vessels was insignificant.

Considering the abnormal findings in renal imaging and laboratory data, the diagnosis of AKI was established, and the patient underwent two episodes of hemodialysis over the next 5 days of admission. However, the second post-dialysis creatinine level stood at 2.92 mg/dL, which was still higher than normal (Table 1).

Due to persistent abnormal renal function without a specific etiology, the decision to obtain a renal biopsy was made on the 7th day of admission. Histopathological evaluation of the kidney biopsy indicated RAVT at the corticomedullary junction (Figures 1A, B).

Following the RAVT diagnosis, tests such as immunologic workup, protein S/C deficiency, anti-phospholipid antibody, and factor V Leiden mutation were done, all of which were normal.

Based on the final diagnosis, the treatment decision was made based on discussions in a consulting board consisting of bioethicists, pharmacists, internists, and nephrologists. We decided to initiate oral anticoagulation therapy for this patient. However, we opted against prescribing Warfarin due to the patient's limited access to healthcare facilities for monitoring blood clotting markers. Therefore, she was commenced on Apixaban 10 mg Bid. The patient's serum creatinine level dropped to 1.63 mg/dL after 7 days of DOAC treatment in the hospital. Upon discharge, the Apixaban dosing was adjusted to 5 mg Bid, and a three-month follow-up visit indicated intact renal function with a regular serum creatinine measurement. A follow-up ultrasound scan did not reveal any hydronephrosis or urinary stasis. The patient expressed

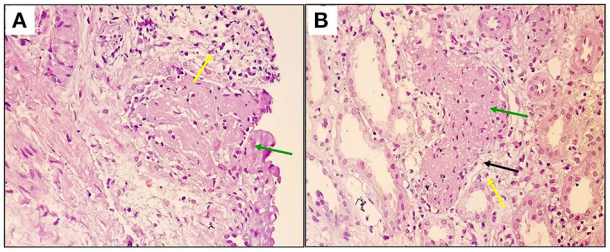

FIGURE 1
Renal arcuate venous thrombus mainly comprises fibrin and some inflammatory cells [green arrows, **(A, B)**], destruction of the endothelial lining [black arrow, **(B)**], and secondary inflammatory reaction, including fibroblastic proliferation and mononuclear cells [yellow arrows, **(A, B)**] close to the thrombosed vessel can be seen at x200 (Hematoxylin and Eosin staining).

her satisfaction with the treatment course and did not complain of unwanted side effects.

Discussion and conclusion

Abnormalities in several elements of the vascular and coagulation systems cause thrombosis. Virchow described thrombosis etiology as the result of irregularities in the vessel wall, platelets, and coagulation proteins. The interaction of these three variables became known as the Virchow triad (19).

RAVT is one of the rarest forms of unusual site venous thromboembolisms (VTEs). To the best of our knowledge, only one previous case series study has demonstrated AKI and RAVT in adults. This study, which evaluated six patients presenting with overt AKI and histopathological findings of RAVT, found that all patients consumed at least moderate amounts of alcohol before showing symptoms (10). However, our case did not report any history of alcohol or illicit substance ingestion.

In the above-mentioned study, several patients also used oral NSAIDs and antibiotics. Overall, it appears that the etiology of renal injury in these cases was due to the ingestion of toxic agents and direct renal injury. In addition, signs of pre-renal etiologies, such as severe dehydration and shock, were absent (10). Similar to these cases, our reported case consumed possibly toxic opium containing traditional herbal medicine compounds. According to the manufacturer, its ingredients include *Zataria multiflora Boiss*, *Allium Sativum*, *Heracleum persicum*, *Satureja hortensis*, *Dianthus*, *Foeniculum vulgare*, and trace amounts of opium (20). However, one striking feature of the patient evaluated in our research is the context in which this patient used the medicinal compounds. This medicine was developed for upper respiratory tract symptom relief in COVID-19 patients. Although our workup revealed negative COVID-19 RT-PCR up to 3 times during admission, the patient declared her respiratory symptoms had become evident concomitant with her husband's diagnosis of COVID-19 around 2 days before the onset of her symptoms. False-negative COVID-19 may have also contributed to the presentation of RVT in our case, considering the unexplained high white blood cell count at admission.

Management of acute RVT is based on the presence of AKI. Some resources propose that those concurrently presenting with RVT and AKI should undergo thrombolytic therapy, whereas those without AKI must be treated with therapeutic doses of anticoagulants (21).

Although anticoagulation with Heparin and Warfarin has been studied in RVT patients, the concept of using DOACs in unusual site VTEs is understudied (6, 22). Apixaban has been formerly shown as a reliable drug in treating venous thromboembolism. A randomized clinical trial of 5395 participants concluded that Apixaban therapy did not show inferior results compared to conventional therapy in venous thromboembolism patients (23). One of the few studies regarding DOACs treatment in the setting of VTE in atypical locations demonstrated that there were no statistically significant differences in VTE recurrence and hemorrhage risk between those treated with DOACs such as Rivaroxaban/Apixaban and those conventionally treated with low molecular weight Heparins such as Enoxaparin (14). Other case reports have also shown the effectiveness of Apixaban in setting RVT without acute renal dysfunction (17). In concordance with other studies, our case shows that RVT may be a consequence of COVID-19 infection or even a feature of long COVID. Other types of DOACs, such as Rivaroxaban, have shown positive results in treating RVT in single case studies (16, 24). To the best of our knowledge, our study is the first to have used Apixaban as a treatment for a rare presentation of RVT in the renal arcuate veins.

A patient-centered survey of 200 individuals with VTE indicated that an overwhelming majority of patients chose DOACs over Vitamin K antagonists. Patients expressed the lack of routine laboratory monitoring, the reduced risk of severe hemorrhage, and fewer drug-food interactions as the most compelling reasons to switch to DOACs (25).

Although liver and renal failure are known to be limiting factors in the usage of many DOACs, pharmacokinetic studies have revealed that there is no need for renal adjustment calculations when using Apixaban (26). The renal safety index of Apixaban was also validated in a study on end-stage kidney disease (ESKD) patients with atrial fibrillation (27). Although some guidelines do not favor using DOACs in the setting of renal failure (28), our experience shows that Apixaban, as an exception, is safely tolerated and effective in treating RAVT.

It is important to note that conclusions regarding drug efficacy should only be drawn in randomized clinical trials. Further histopathological studies on patients with toxic substance ingestion and AKI are necessary to elucidate whether or not RAVT is a single and particular entity with identifiable causes.

Data availability statement

Data reported in this manuscript are available upon reasonable request from the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Shiraz University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study. 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

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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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