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CASE REPORT

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Late-onset renal TMA and tubular injury in cobalamin C disease: a report of three cases and literature review

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Abstract

Background Mutation of *MMACHC* gene causes cobalamin C disease (cblC), an inherited metabolic disorder, which presents as combined methylmalonic aciduria (MMA-uria) and hyperhomocysteinaemia in clinical. Renal complications may also be present in patients with this inborn deficiency. The most common histological change is thrombotic microangiopathy (TMA). However, to our acknowledge, renal tubular injury in the late-onset presentation of cblC is rarely been reported. This study provides a detailed description of the characteristics of kidney disease in cblC deficiency, aiming to improve the early recognition of this treatable disease for clinical nephrologists.

Case presentation Here we described three teenage patients who presented with hematuria, proteinuria, and hypertension in clinical presentation. They were diagnosed with renal involvement due to cblC deficiency after laboratory tests revealing elevated serum and urine homocysteine, renal biopsy showing TMA and tubular injury, along with genetic testing showing heterogeneous compound mutations in *MMACHC*. Hydroxocobalamin, betaine, and L-carnitine were administered to these patients. All of them got improved, with decreased homocysteine, controlled blood pressure, and kidney outcomes recovered.

Conclusions The clinical diagnosis of cblC disease associated with kidney injury should be considered in patients with unclear TMA accompanied by a high concentration of serum homocysteine, even in teenagers or adults. Early diagnosis and timely intervention are vital to improving the prognosis of cobalamin C disease.

Clinical Trial Number Not applicable.

Keywords Thrombotic microangiopathy, Cobalamin C disease, *MMACHC*, Renal tubular injury, Homocystinuria

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Background

Combined methylmalonic aciduria (MMA-uria) and hyperhomocysteinaemia, cobalamin C (cblC) type, is the most common genetic type of functional cobalamin (a cofactor form of vitamin B12) deficiency, which is a kind of inherited metabolic disorder presented with diverse clinical manifestations combining multisystem damage [1, 2]. Patients with early-onset cblC may present in the first month of life with lethargy, hypotonia, poor oral intake, and failure to thrive [3]. While patients with late-onset cblC may present neuropsychiatric symptoms, like lower limb weakness, psychiatric disturbances, gait instability, or brain or spinal cord changes by imaging [4]. Kidney injury associated with cblC is uncommon [1]. Limited research works showed renal histopathology with glomerular lesions typical of thrombotic microangiopathy (TMA) [5]. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are the 2 most frequent causes of TMA. Other causes of TMA include drugs, malignancies, pregnancy, autoimmune diseases, or malignant hypertension [5, 6]. Metabolic disease associated TMA are often ignored or hard to diagnose. Here we present three cases of kidney involvement in patients with cblC, presented with TMA and tubular injury in kidney biopsy. We also conducted a literature review of cblC disease with renal involvement in a summary of clinical and pathological impairment, aiming to enhance awareness and understanding of this rare, but treatable disease.

Case presentation

Patient 1

A 15-year-old young boy was admitted to our department due to proteinuria and hematuria with elevated blood pressure (170/120 mmHg) for 1 week. The laboratory examination showed macrocytic anemia (hemoglobin 9.3 g/dl, MCV 105.3 fl.), proteinuria (3+), and hematuria (20–30 cells/HPF). The 24-hour urinary protein was 2.12 g/day (total urine volume 500 ml) with decreased serum albumin level of 34.4 g/L. Serum creatinine (SCr) was 110.2 μmol/L (reference range: 56–102 μmol/L). Serum level of homocysteine (HCY) was over 200 μmol/L (reference range: 6–17 μmol/L), which exceeded the detection limit in routine test. He had a comparatively low level of complement component (C3 0.587 g/L, reference range: 0.6–1.5 g/L; C4 0.106 g/L, reference range: 0.12–0.36 g/L) and a low titer of positive antinuclear antibody (ANA) (1:100). However, no systemic immune or infection related disease was observed. He had impaired urine concentration function, with significantly low morning urinary osmotic pressure (310 mOsm/kg, reference range: 600–1000 mOsm/kg), and blood osmotic pressure was normal (293 mOsm/kg, reference range: 275–305 mOsm/kg). Urine glucose was negative and urine acidification examination was normal, without hypophosphatemia and hypouricemia. Schistocytes on the blood smear could be seen, accounting for 1.2%, with thrombocytopenia (platelet 118,000/mm^3), and increased lactate dehydrogenase (LDH 573 IU/L), which indicated the microangiopathic hemolytic anemia (MAHA), without any history of thrombosis. However, von Willebrand factor protease (ADAMTS13) and the concentration of factor H were both normal, and the anti-factor H antibody was negative..

He was diagnosed with cblC 2 months after his birth, and treated with hydroxocobalamin, L-carnitine and betaine ever since. Comprehensive genetic analyses revealed compound heterozygous variants *c.609 G>A (p.W203*)* (The American College of Medical Genetics and Genomics, ACMG classification: pathogenic) and *c.658_660del (p.K220del)* (ACMG classification: likely pathogenic) mutation in the *MMACHC* gene (Fig. 1). He developed well in spite with stable disease. He had no signs of involvement of intelligence, sensibility or central nervous system symptoms, such as seizures, ataxia, or hypotonia, until he interrupted his therapy 4 months before admission.

A renal biopsy was performed (Fig. 2). Light microscopic examination showed that 1/28 glomeruli was ischemic and sclerotic. The rest of the glomeruli showed mild mesangial expansion, accompanied by segmental endothelial cell proliferation. The glomerular basement membrane thickened diffusely, with the formation of "double contours". The tubules displayed loss of brush border with epithelial simplification. Direct immunofluorescence revealed trace staining for segmental granular deposition of IgA (+) and IgM (+) on mesangial area, and negative for IgG, C3, and C1q. He was diagnosed with renal TMA and acute tubular injury as the renal complication of cblC. Electron microscopy confirmed the diagnosis, and no enlarged mitochondria was detected. The patient was treated with hydroxocobalamin (3 mg/day, i.m.), betaine (9 g/day, p.o.), L-carnitine (2 g/day, p.o.) as well as Vitamin AD and vitamin B compounds daily. Besides, angiotensin receptor blockers and calcium channel blockers combinations were used to treat hypertension. After 6 weeks of treatment, his blood pressure, hemoglobin, LDH and urine protein returned to normal. HCY decreased to 85.56μmol/L and SCr decreased to 65 μmol/L which indicated that an event of acute kidney disease occurred in this patient.

Patient 2

A 15-year-old boy was admitted to our department due to proteinuria and hematuria for 1 year. His blood pressure was 135/85 mmHg. Urinary protein excretion was 2.05 g/day (urine volume 1000 ml) and his SCr was 72 μmol/L (reference range 44–133 μmol/L). Urinary

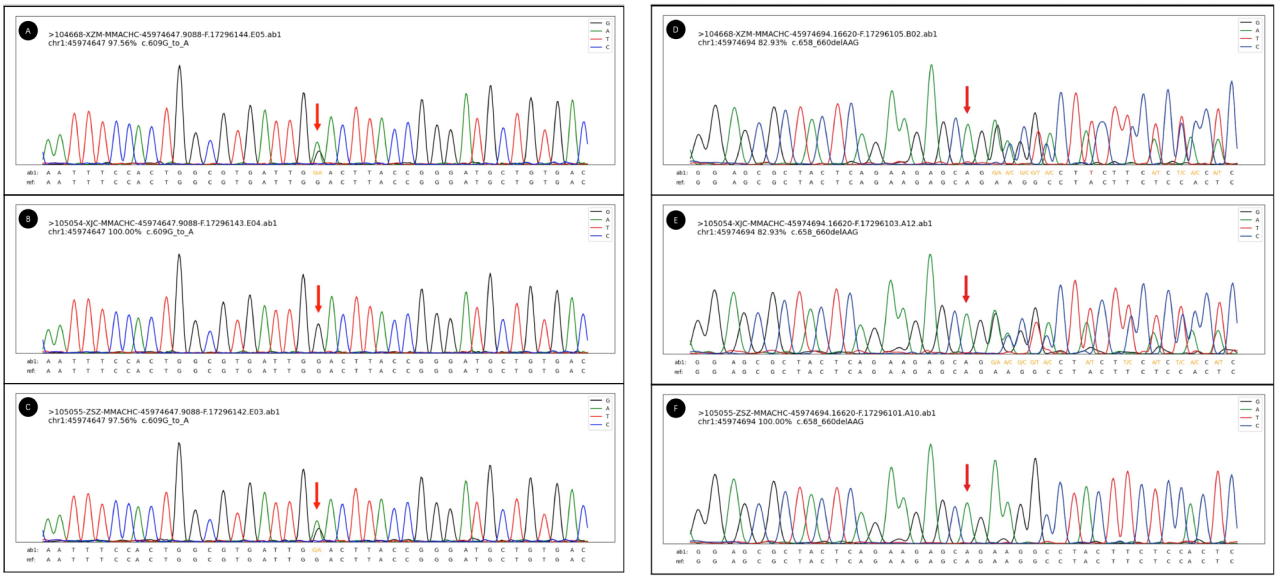

Fig. 1 Sanger electropherogram figure of *MMACHC* mutation in patient 1. A to C and D to F shows the mutated locus of patient 1, his father, and his mother on *c.609 G > A (p.W203*) and c.658_660del (p.K220del)*, separately

N-acetyl-beta-D-glucoaminidase (NAG) was elevated to 18.7 U/L. HCY was 149.01 μmol/L, which was also significantly increased. Urine glucose was negative, along with hyperuricemia but normal serum phosphorus. ANA was positive (1:320). Anti-dsDNA, anticardiolipin antibodies, and anti-β2-GP1 antibodies were all negative. Echocardiography showed an enlarged right heart with pulmonary arterial hypertension (86 mmHg). The level of hemoglobin and platelet count were both normal. There were no evidence of MAHA and no signs of thrombotic event in examinations. Renal biopsy showed TMA, combined with focal segmental glomerulosclerosis (FSGS) like lesions. Tubular epithelial cells presented with vacuolar and granular degeneration.

He went to the other medical center due to dyspnea 1 year ago. During hospitalization, examination showed pulmonary arterial hypertension and megaloblastic anemia. Electromyography (EMG) and nerve conduction velocity (NCV) showed peripheral nerve injury in the upper and lower limbs. Genetic analyses showed compound heterozygous variants of the *c.80 A > G (p.Q27R)* (ACMG classification: pathogenic) and *c.609G > A (p.W203X)* (ACMG classification: pathogenic) in *MMACHC* gene, which confirmed the diagnosis was MMA-uria and hyperhomocysteinaemia (cblC type). The patient was 195 cm in height and weighed 70 kg but his physical strength was worse than his peers, and he had not attended physical education classes since the fifth grade of primary school. Intelligence Quotient (IQ) test showed he has a normal IQ score of over 90.

Treatment with mecobalamin (3 mg/day, p.o.), cobamamide (3 mg/day, i.m.), folic acid (5 mg/day, p.o.), betaine (9 g/day, p.o.), L-carnitine (2 g/day, p.o.), as well as Vitamin AD compounds and vitamin B supplements. Lotensin (10 mg/day, p.o.) was used to anti-hypertension and ambrisentan (5 mg/day, p.o.) was also used to reduce pulmonary artery pressure. Within the next 10 days, the serum HCY was decreased to 136.22 μmol/L and 24 h-urinary protein excretion was reduced to 1.18 g/day (total urine volume 650 ml). At the last follow-up, two months after the discharge, the patient's serum HCY was decreased to a satisfactory level of 50.13 μmol/L, and blood pressure was well controlled under antihypertensive agents.

Patient 3

A 16-year-old boy without significant medical history presented with severe hypertension (up to 180/116 mmHg) with the chief complaint of a decrease in activity tolerance, mucosal hemorrhage, and oliguria. Further examination showed anemia (Hb 6.3 g/dl) with schistocytes, thrombocytopenia (90,000/mm^3), kidney injury (SCr 197 μmol/L), proteinuria, elevated lactate dehydrogenase (LDH 779 U/L) and abnormal NT-proBNP (6152 pg/ml). Ultrasonography revealed enlargement of left atrial and the thickening of left ventricular wall and splenomegaly. Renal biopsy showed typical signs of TMA in glomerulus, which presented as duplication of the glomerular basement membrane (GBM), endothelial swelling, mesangiolysis and intraglomerular thrombi, along with swelling of the tubular epithelium, and a patchy infiltration of lymphocytes and monocytes was present within the interstitial area, with interstitial fibrosis. ANA, serum complement level, H factor and ADAMTS 13

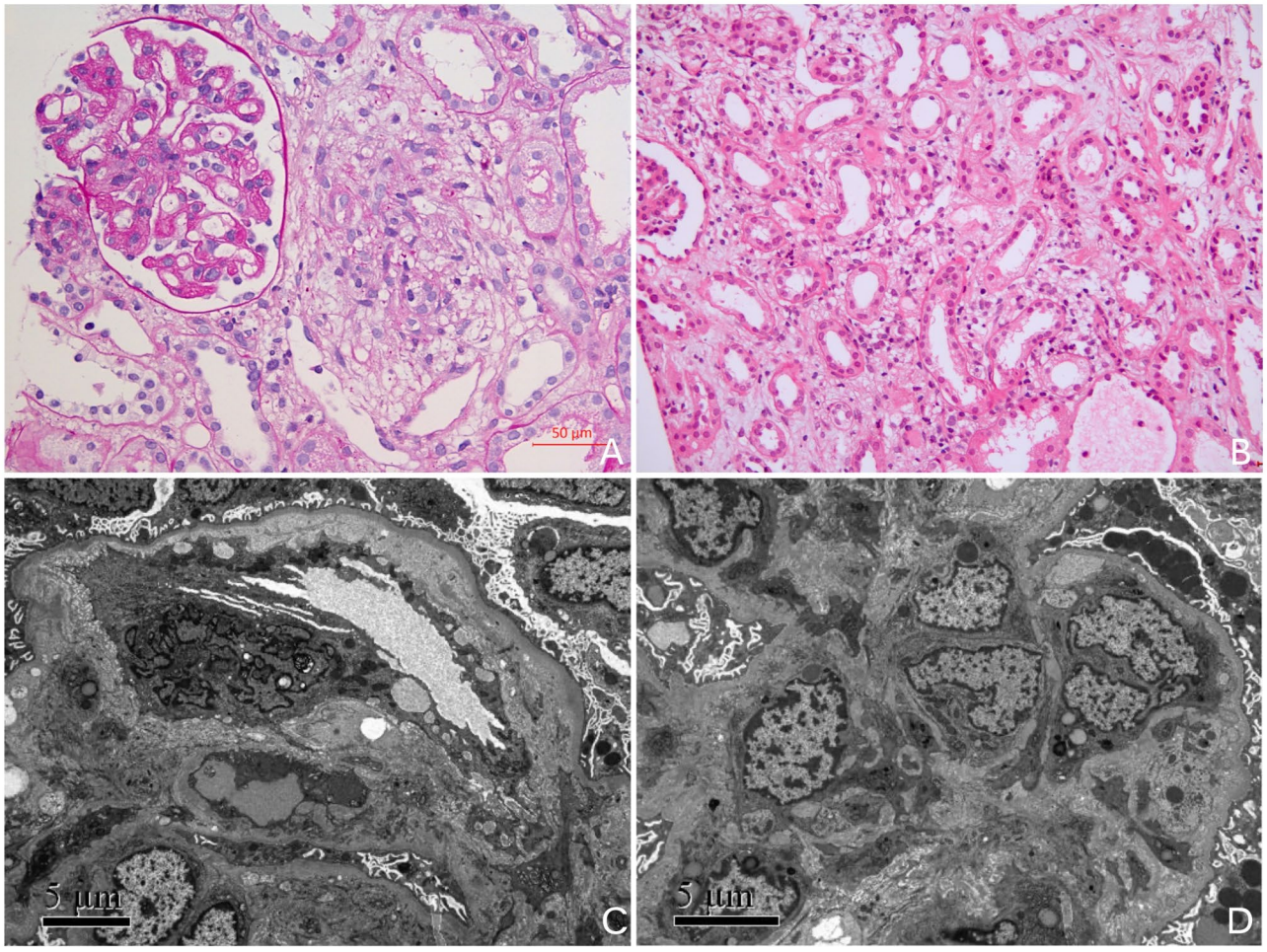

Fig. 2 Kidney biopsy findings. (**A**) The glomerulus exhibited segmental endothelial cell proliferation with diffusely thickened glomerular basement membrane and the formation of 'double contours', and a granuloma consisted of mainly foam cells at beside interstitium (PAS ×400). (**B**) The loss of brush border with epithelial simplification of tubular epithelia was presented, along with focal infiltration of lymphocyte and mononuclear cells in renal interstitium (HE×400). (**C**) Electron microscopy showed widening of subendothelial area of glomerular basement membrane with narrowed cavity of capillary loops (original magnification ×5,000). (**D**) Proliferation of mesangial cells and endothelial cells with occlusion of glomerular capillary lumen was observed (original magnification×6,000)

activity were normal. There was no evidence of any bacterial and viral infection, including HIV, as well as the effect of drugs or toxic exposure. Glucocorticoid, plasmapheresis and antihypertensive drugs (including RAASi) were used for TMA therapy. However, although hemolysis was rapidly controlled with normalization of the LDH and platelet count, his kidney injury was still progressive to end-stage kidney disease. In addition, he also presented with renal tubular acidosis and persistent hyperkalemia. This phenomenon forced us to continue searching for the cause of TMA.

The intellectually disabled sister in family history and a marked rise in serum level of HCY (247.8 μmol/L) put the focus on cobalamin C metabolism. A higher level of urine HCY (65.71 μmol/L) supported our suspicion. Nutritional B12 deficiency was excluded by a normal serum level. However, chromatographic evaluation of the urine showed methylmalonic aciduria. A cobalamin C (cblC) deficiency presented with MMA-uria and hyperhomocysteinaemia was subsequently confirmed by genetic testing of the two heterozygous likely pathogenic mutations of *c.1 A>G (p.Met1?)* (ACMG classification: likely pathogenic) and *c.80 A>G (p.Q27R)* (ACMG classification: likely pathogenic) in the *MMACHC* gene. The same genetic mutation was also found in the blood sample of his mother and father, respectively.

After a definite diagnosis of cblC deficiency, the patient was treated with hydroxocobalamin, betaine, calcium folinate and L-carnitine. After one month of therapy, serum HCY decreased to 83 μmol/l, and urine HCY decreased to 28 μmol/l, while the patient was still hemodialysis-dependent. It was reassuring that after 10 months of drug therapy, the level of hemoglobin, platelet and LDH recovered. Furthermore, this patient was finally

dialysis-free with the level of SCr maintained at185 μmol/L.

Discussion and conclusions

Combined MMA-uria and hyperhomocysteinaemia, cobalamin C (cblC) type, is the most common genetic type of functional cobalamin deficiency. This metabolic disorder is characterized by marked heterogeneity of the neurocognitive disease and variable extra-central nervous system involvement, including renal, cardiovascular and ocular [1]. Neonates typically show lethargy, seizures and muscular hypotonia. Visual impairment such as nystagmus on the background of retinopathy or optic atrophy exhibit in up to 50% of infants. Nevertheless, older children, adolescents and adults may present with acute or chronic behavioral or psychiatric, cognitive impairment, signs of peripheral neuropathy and ataxia or rarely venous thromboembolism [2]. The pathophysiology of cblC deficiency is not comprehensively understood and it is likely that the synergistic effect of different mechanisms [7]. Previous studies illustrated that cobalamin C defect causes the impaired conversion of dietary cobalamin into its two metabolically active forms, methylcobalamin and adenosylcobalamin. Methylcobalamin is the cofactor for methionine synthase, which catalyzes the remethylation of homocysteine into methionine in the cytoplasm and is also responsible for the regeneration of methionine from homocysteine. Adenosylcobalamin is the cofactor for the methylmalonyl-CoA mutase, which converts methylmalonyl-CoA into succinyl-CoA in mitochondria. When these two reactions are impaired, accumulation of homocysteine and MMA could appear, as well as the reduction synthesis of methionine [7–9]. Toxicity of methylmalonate and homocysteine may play a crucial role in mitochondrial energy metabolism and vascular endothelial injury, which is responsible for the multisystem organ involvement [5, 7].

We have herein described three patients, who were presented with consistent clinical features of proteinuria and hematuria, and renal function ranged from normal to kidney dysfunction in their teenage. Renal biopsies of all 3 cases were presented as glomerular lesions of TMA and acute tubular injury at the same time (Table 1). Even though there was no evidence of MAHA in patient 2, we could still find TMA lesions in his kidney. Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are the 2 most frequent causes of TMA. Other causes of TMA include malignant hypertension, infection, autoimmune diseases, or drugs that also should be considered for differentiation of TMA. However, certain laboratory investigations, such as infectious, endocrinological, and immunological factors were performed to exclude the above potential causes. In a previous study, Lemoine M et al. revealed arteriolar and glomerular TMA in cblC patients and showed that GBM vacuoles and IgM deposition were significantly more frequent, compared to a control population with cblC-independent TMA [5]. In the present study, we showed typical glomerular TMA lesions with thickening of capillary wall in all patients and intraglomerular thrombi in one patient, and all of them presented typical tubular necrosis. Obviously, in all these cases, the homocysteine was elevated significantly, which could be a clue for the differential diagnosis of cblC. The diagnosis of cblC disease is mainly based on biochemical hallmarks of elevated plasma and urine methylmalonic acid, hyperhomocysteinaemia, low blood methionine and genetic testing. *c.80 A>G* and *c.609G>A* were two common mutations in Chinese cblC type patients and were reported to be associated with late-onset cblC disease [10]. This deficiency is a treatable disease and timely recognition of cblC deficiency is of utmost importance for treatment. Patients with elevation of biochemical hallmarks that are associated with severe disease should be treated immediately and the acute management of patients even cannot wait for the results of genetic analyses. The supplements of hydroxocobalamin, betaine, and L-carnitine in our three patients resulted in a significant decrease in serum HCY and urinary protein, as well as significant kidney function improvement. One patient reached complete kidney function recovery at the last follow-up and the other patient still remains CKD but not dependent on dialysis.

Two distinct phenotypes have been defined in terms of age of onset. Early-onset patients present in infants with multisystem disorders, including neurological, hematological abnormalities, ocular, renal, gastrointestinal, cardiac, and pulmonary manifestations and the survivors may have severe neurological impairment [11, 12]. Late-onset cblC disease was recognized in the 1980s (Shinnar and Singer 1984) and the term has been historically applied to patients that have overt symptoms after 4 years of age [4]. Patients usually present with a milder clinical phenotype characterized by acute or slowly progressive neurological symptoms, behavioral disturbances, and chronic kidney disease [7, 12]. HUS and pulmonary hypertension are often the main presenting symptoms in preschool children with late onset cblC. About 90% of patients which have been reported had an early onset of disease, but the late onset form is much rarer. Kalantari et al. presented an emblematic case of adult-onset cblC deficiency with the age of 45 at the onset of disease, who is the oldest patient reported up to now [13]. Despite therapeutic improvements in the last decades, chronic organ manifestations occur in many patients [12], especially in interrupted or irregular therapy. Patients with renal disease mostly had clinical features of hematuria and proteinuria (also up to the nephrotic range), hypertension (also malignant hypertension), chronic renal failure (from

Table 1 Clinical characteristics of the 3 cases at initial presentation

	Patient 1	Patient 2	Patient 3
Age (yr)	15	15	16
Sex	Male	Male	Male
Clinical Presentation			
Proteinuria	Yes	Yes	Yes
Hematuria	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes
Pulmonary arterial hypertension	No	Yes	No
Oliguria	No	No	Yes
Hemorrhagic event	No	No	Yes
Laboratory Examination			
Hemoglobin (g/dl)	9.3	15.0	6.3
Platelets (number/mm^3)	118,000	295,000	90,000
Schistocytes	Yes	No	Yes
LDH (IU/L)	573	194	779
Serum albumin (g/L)	34.4	40.8	33.0
Serum creatinine (μmol/L)	110.2	72	197
C3 (g/L)	0.587	Normal	Normal
C4 (g/L)	0.106	Normal	Normal
Serum HCY (μmol/L)	287.0	149.0	247.8
Urine HCY (μmol/L)	NA	NA	65.7
Urine MMA/Cr (mmol/mol, normal range: 0.2–3.6)	8.36	12.66	62.29
24-hour urine protein (g/day)	2.12	2.05	3.28
Renal Pathology			
Ischemia	Yes	Yes	Yes
Endothelial proliferation and swelling	Yes	Yes	Yes
Mesangial lysis	No	No	Yes
GBM thickening and duplication	Yes	Yes	Yes
Endocapillary glomerular thrombi	No	No	No
Intra-arterial thrombi	No	No	Yes
Capillary wall thickening	Yes	Yes	Yes
Tubular injury	Yes	Yes	Yes
Interstitial inflammation	Yes	No	Yes
Interstitial infiltered by foaming cells	Yes	No	No
Immunofluorescence	IgA (+), IgM (+), λ (+)	IgA (+), C3 (+)	IgM (+)
Management			
Hydroxocobalamin	Yes	No	Yes
Mecobalamin	No	Yes	No
Cobamamide	No	Yes	No
Betaine	Yes	Yes	Yes
Folic acid	No	Yes	Yes
L-carnitine	Yes	Yes	Yes
Vitamin AD and B supplements	Yes	Yes	No
Other treatments	No	Ambrisentan to reduce PA pressure	No
Outcome after treatment			
Duration of treatment	6 weeks	2 months	10 months
Kidney function	Normal	Normal	CKD remaining
SCr at last follow-up (μmol/L)	107.21	72.38	169
eGFR at last follow-up (ml/min/1.73m^2)	88.5	142.31	50.34
CKD stage at last follow-up	stage 2	stage 1	stage 3a
Dialysis	NA	NA	Independent

C3, complement component 3; C4, complement component 4; CKD, chronic kidney disease; CKD remaining means estimated glomerular filtration rate lower than 60 ml/min/1.73m^2; Cr, creatinine; eGFR, estimated glomerular filtration rate (CKD-EPI), HCY, homocysteine; LDH, lactate dehydrogenase; MMA, methylmalonic acid; NA, not available; PA, pulmonary artery; SCr, Serum creatinine

mild to severe), even some with intravascular hemolysis. Kalantari and his colleagues also performed a systemic review including 45 adult onset patients, to find glomerular nephropathy, kidney failure, proteinuria and HUS still common in renal manifestation [13]. Renal biopsies predominantly demonstrate thrombotic microangiopathy [1, 12], including glomerular fibrin thrombi, endothelial swelling, and duplication of the glomerular basement membrane, but also membranous nephropathy associated to cblC disease has been reported recently [14]. We present a summary of clinical and pathology findings of cblC disease with renal involvement in recent reviews and case reports (Table 2). The etiology of TMA in patients with cobalamin C defects remains unknown. It has been demonstrated that hyperhomocysteinaemia could induce damage to endothelial cells [1, 19]. Impairment of the nitric oxide-dependent inhibition of platelet aggregation or the procoagulant state of the endothelium leads to the formation of microthrombi [20].

In patients with isolated MMA, chronic tubulointerstitial nephritis with progressive impairment of renal function could be observed [12]. Some patients with isolated MMA have proximal renal tubular acidosis [21]. However, cblC is hardly reported with renal tubular injury, like tubulointerstitial nephritis and interstitial fibrosis. Our three patients all had clinical evidence of renal tubular injury, which may lead to dysfunction of urine concentration and/or acidification. Kidney biopsy findings also

Table 2 Clinical and pathological impairment of cblC disease with renal involvement

Source	Number of subjects	Clinical Presentation	Renal Histology	Management	Outcome
Cornec-Legall et al. 2014 [15]	1 patient	malignant hypertension kidney failure	glomerular and arteriolar TMA	Eculizumab hydroxycobalamin oral anhydrous betaine folinic acid	hemodialysis stopped kidney function remained stable
Koenig et al. 2015 [16]	1 patient	nephrotic syndrome macrocytic anemia	TMA with ischemic glomerular collapse tubulointerstitial fibrosis	hydroxycobalamin antihypertensive treatment (ACEi) folinic acid	plasma homocysteine decreased anemia improved reduction of proteinuria
Grangé et al. 2015 [17]	1 patient	renal failure nephrotic syndrome hematuria hypertension hemolytic anemia PAH	renal TMA	hydroxycobalamin betaine folinic acid	stop dialysis with serum creatinine stable around 147 μmol/L
Beck et al. 2017 [1]	36 patients	proteinuria and hematuria nephrotic syndrome intravascular hemolysis arterial hypertension	glomerular TMA (including glomerular fibrin thrombi, endothelial swelling, and duplication of GBM)	hydroxycobalamin cyanocobalamin complement-targeted therapy (including plasma exchange and Eculizumab) RRT	54% clinical recovery 44% overall mortality
Lemoine et al. 2018 [5]	7 patients	hypertension edema proteinuria PAH thromboembolic events	glomerular TMA arteriolar TMA remodeling of GBM (including duplication and vacuolar of GBM) interstitial fibrosis tubular atrophy acute tubular necrosis	hydroxycobalamin betaine folinic acid plasma exchange Eculizumab	3 patients recovered and weaned off dialysis 2 patients received kidney transplant 1 patient dialysis-dependent 1 patient died
Philipponnet et al. 2020 [18]	1 patient	acute kidney failure proteinuria	renal TMA	hydroxycobalamin folinic acid betaine levocarnitine plasma exchange Eculizumab Rituximab	kidney function recovered
Wang, et al. 2022 [14]	1 patient	proteinuria and hematuria edema	membranous nephropathy	hydroxocobalamin betaine L-carnitine	urinary protein concentration and erythrocyte count were within the reference ranges

ACEi, angiotensin converting enzyme inhibitor; GBM, glomerular basement membrane; PAH, pulmonary arterial hypertension; RRT, renal replacement therapy

confirmed tubulointerstitial nephritis with inflammation and patchy interstitial fibrosis, which is presumably associated with toxic metabolites interfering with intrarenal mitochondrial metabolism [22]. Since the urinary excretion of MMA and other putatively toxic metabolites of alternative propionate oxidation (e.g. 2-methylcitrate) diminishes with decreasing kidney function and thus accumulating toxic compounds could foster the naturally occurring disease progression despite hydroxocobalamin supplementation [23]. However, we assumed that these tubulointerstitial changes were too mild to account for the severity of the renal disease.

Treatment strategies usually consist of a combined approach including utilizing hydroxycobalamin to increase intracellular cobalamin and maximize deficient enzyme activities, betaine to provide a substrate for the conversion of homocysteine into methionine through betaine-homocysteine methyltransferase, and folic acid to enhance remethylation pathways [12]. However, there is no proven efficacy for carnitine and methionine supplementation, and dietary protein restriction in these patients [7]. Urinary methylmalonic acid excretion was often used to assess cobalamin responsiveness before and after administration of cobalamin [24]. The reported outcomes of MMA cases vary in the literature and range from insignificant to initiation of renal replacement therapy (RRT), which depends mainly on the type of disease, the onset, and clinical compliance [25]. Mortality was higher in infants (57%) compared with later-onset disease (35%), resulting in an overall mortality rate of 44% [1]. Some patients experienced complete recovery of kidney function, while the others had residual kidney dysfunction with persistent proteinuria and hematuria [25, 26] or some remaining dialysis-dependent [1]. However, when recognized and treated at an early stage, complete clinical recovery is possible.

The clinical diagnosis of cblC disease associated with kidney injury should be considered in patients with unclear TMA accompanied with a high concentration of serum homocysteine, even in teenagers or adults. Dosage of MMA and methionine should be tested to complete diagnostic work-up and to discriminate among the different forms of remethylation disorders. MMA in (fresh or optimally stored) urine or blood is the most sensitive intracellular marker. However, limitation should be noticed that urinary MMA is unreliable in individuals with renal functional impairment [2]. Additionally, it is significant to remind that microangiopathic nephropathy can be present in the complete absence of the laboratory alterations typical of TMA [13]. From a diagnostic standpoint, it would be important to perform genetic analysis in patients with a suspected intracellular cobalamin disorder, once homocysteine, methionine and MMA levels have been measured. Awareness should be taken for this rare, but treatable disease.

Abbreviations

ADAMTS13	Von Willebrand factor protease
ANA	Antinuclear antibody
cblC	Cobalamin C disease
dsDNA	Double-stranded DNA
FSGS	Focal segmental glomerulosclerosis
Hb	Hemoglobin
HCY	Homocysteine
Ig	Immunoglobin
LDH	Lactate dehydrogenase
MAHA	Microangiopathic hemolytic anemia
MMA-uria	Methylmalonic aciduria
NAG	N-acetyl-beta-D-glucoaminidase
RAASi	Renin- angiotensin-aldosterone System inhibitors
RRT	Renal replacement therapy
SCr	Serum creatinine
TMA	Thrombotic microangiopathy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03774-w.

Supplementary Material 1: **Supplementary Fig.1**. Sanger electropherogram figure of *MMACHC* mutation in patient 2. A to C and D to F shows the mutated locus of patient 2, his father, and his mother on *c.609G > A (p.W203X) and c.80 A > G (p.Q27R)*, separately

Supplementary Material 2: **Supplementary Fig.2**. Sanger electropherogram figure of *MMACHC* mutation in patient 3. A to C and D to F shows the mutated locus of patient 3, his father, and his mother on *c.1 A > G (p.Met1?) and c.80 A > G (p.Q27R)*, separately

Supplementary Material 3: Supplementary Table 1. Biochemical Hallmarks of the 3 cases

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Not available.

Author contributions
DB, HY, and YY analyzed and interpreted the patient data and were major contributors to writing the manuscript. SW and XZ performed interpretation of pathological data. YL, TS, RX, CL and FZ performed interpretation of the clinical data and substantively revised it. All authors contributed to the article and approved the submitted version.

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

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by Peking University First Hospital, approval number: 2017[1333]. The patients/participants provided their written informed consent to participate in this study.

Consent for publication
Written informed consent was obtained from the individuals and their parents for the publication of any potentially identifiable images or data included in this article.

Competing interests
The authors declare no competing interests.

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References

1. Beck BB, van Spronsen F, Diepstra A, et al. Renal thrombotic microangiopathy in patients with cblC defect: review of an under-recognized entity. Pediatr Nephrol. 2017;32(5):733–41.
2. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21–48.
3. Ahrens-Nicklas RC, Whitaker AM, Kaplan P, et al. Efficacy of early treatment in patients with cobalamin C disease identified by newborn screening: a 16-year experience. Genet Med. 2017;19(8):926–35.
4. Carrillo-Carrasco N, Chandler RJ, Venditti CP. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. J Inherit Metab Dis. 2012;35(1):91–102.
5. Lemoine M, Francois A, Grange S, et al. Cobalamin C Deficiency induces a typical histopathological pattern of renal arteriolar and glomerular thrombotic microangiopathy. Kidney Int Rep. 2018;3(5):1153–62.
6. Genest DS, Patriquin CJ, Licht C. Renal thrombotic microangiopathy: a review. Am J Kidney Dis. 2023;81(5):591–605.
7. Martinelli D, Deodato F, Dionisi-Vici C, Cobalamin C. Defect: natural history, pathophysiology, and treatment. J Inherit Metab Dis. 2011;34(1):127–35.
8. George AK, Homme RP, Majumder A, et al. Hydrogen sulfide intervention in cystathionine-β-synthase mutant mouse helps restore ocular homeostasis. Int J Ophthalmol. 2019;12(5):754–64.
9. Huemer M, Baumgartner MR. The clinical presentation of cobalamin-related disorders: from acquired deficiencies to inborn errors of absorption and intracellular pathways. J Inherit Metab Dis. 2019;42(4):686–705.
10. Wen LY, Guo YK, Shi XQ. Pulmonary hypertension in late-onset Methylmalonic Aciduria and Homocystinemia: a case report. BMC Pediatr. 2020;20(1):243.
11. Liu MY, Yang YL, Chang YC, et al. Mutation spectrum of MMACHC in Chinese patients with combined methylmalonic aciduria and homocystinuria. J Hum Genet. 2010;55(9):621–6.
12. Morath MA, Horster F, Sauer SW. Renal dysfunction in methylmalonic acidurias: review for the pediatric nephrologist. Pediatr Nephrol. 2013;28(2):227–35.
13. Kalantari S, Brezzi B, Bracciamà V, et al. Adult-onset CblC deficiency: a challenging diagnosis involving different adult clinical specialists. Orphanet J Rare Dis. 2022;17(1):33.
14. Wang Q, Wang Q, Gao Y, et al. Case Report: Membranous Nephropathy secondary to Cobalamin C Disease. Front Med (Lausanne). 2021;8:807017.
15. Cornec-Le Gall E, Delmas Y, De Parscau L, et al. Adult-onset eculizumab-resistant hemolytic uremic syndrome associated with cobalamin C deficiency. Am J Kidney Dis. 2014;63(1):119–23.
16. Koenig JC, Rutsch F, Bockmeyer C, et al. Nephrotic syndrome and thrombotic microangiopathy caused by cobalamin C deficiency. Pediatr Nephrol. 2015;30(7):1203–6.
17. Grangé S, Bekri S, Artaud-Macari E, et al. Adult-onset renal thrombotic microangiopathy and pulmonary arterial hypertension in cobalamin C deficiency. Lancet. 2015;386(9997):1011–2.
18. Philipponnet C, Desenclos J, Brailova M, et al. Cobalamin c deficiency associated with antifactor h antibody-associated hemolytic uremic syndrome in a young adult. BMC Nephrol. 2020;21(1):96.
19. Bernards J, Doubel P, Meeus G, et al. Hyperhomocysteinemia: a trigger for complement-mediated TMA? Acta Clin Belg. 2021;76(1):65–9.
20. Vaisbich MH, Braga A, Gabrielle M, et al. Thrombotic microangiopathy caused by methionine synthase deficiency: diagnosis and treatment pitfalls. Pediatr Nephrol. 2017;32(6):1089–92.
21. Wolff JA, Strom C, Griswold W, et al. Proximal renal tubular acidosis in methylmalonic acidemia. J Neurogenet. 1985;2(1):31–9.
22. Brunelli SM, Meyers KE, Guttenberg M, et al. Cobalamin C deficiency complicated by an atypical glomerulopathy. Pediatr Nephrol. 2002;17(10):800–3.
23. Haarmann A, Mayr M, Kolker S, et al. Renal involvement in a patient with cobalamin a type (cblA) methylmalonic aciduria: a 42-year follow-up. Mol Genet Metab. 2013;110(4):472–6.
24. Brennerova K, Skopkova M, Ostrozlikova M, et al. Genetic testing is necessary for correct diagnosis and treatment in patients with isolated methylmalonic aciduria: a case report. BMC Pediatr. 2021;21(1):578.
25. Chen M, Zhuang J, Yang J, et al. Atypical hemolytic uremic syndrome induced by CblC subtype of methylmalonic academia: a case report and literature review. Med (Baltim). 2017;96(43):e8284.
26. Chen RY, Li XZ, Lin Q, et al. Proteinuria as a presenting sign of combined methylmalonic acidemia and homocysteinemia: case report. BMC Med Genet. 2020;21(1):183.

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