Collapsing glomerulopathy as a rare cause of rapidly progressive renal failure in adolescence: two case reports

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Case presentations

Case 1

A 17-year-old male was referred to our institution in January 2016 due to elevated serum creatinine level of 1.85 mg/dL and nephrotic proteinuria level of 6839 mg/day. He had a history of epilepsy and had used various antiepileptic drugs (phenobarbital, valproic acid, and carbamazepine) from the ages 3 to 14 years. Physical examination revealed lower extremity oedema and a blood pressure of 140/90 mm Hg. Laboratory tests on admission showed a blood urea nitrogen level of 24 mg/dL, serum creatinine level of 1.68 mg/dL and a serum albumin level of 2.7 g/dL. Urine microscopy revealed three red blood cells per high-power field. A 24-hour urine collection revealed massive proteinuria level of 10.957 mg/day (296 mg/m^2/h). Serum complement levels were normal and autoimmune tests (antinuclear antibodies, anti–double-stranded DNA antibodies, anti–glomerular basal membrane antibodies, and anti-neutrophil cytoplasmic antibodies) were negative. Viral serology, including hepatitis B virus, hepatitis C virus, human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, and parvovirus, was also negative. Abdominal ultrasound revealed increased echogenicity in the renal parenchyma.

Treatment with enalapril at a dose of 0.4 mg/kg/day was started. Kidney biopsy was performed on the seventh day after admission and showed compatibility with collapsing glomerulopathy (CG) [Fig 1]. Methylprednisolone boluses of 1 g were administered for 5 consecutive days, followed by oral prednisone at a dose of 60 mg/m^2/day. By the 15th day, serum creatinine levels were at 2.1 mg/dL, serum albumin level at 1.9 g/dL, and 24-hour urine protein level at 17.8 g/day. Mycophenolate mofetil was added to the treatment regimen. On the 40th day, serum creatinine level had increased to 4.2 mg/dL with proteinuria of 13.3 g/day, leading to the initiation of rituximab and tapering of prednisolone. By the 60th day, mycophenolate mofetil was discontinued due to leukopenia; however, the patient had completed the 4 doses of weekly 375 mg/m^2/dose

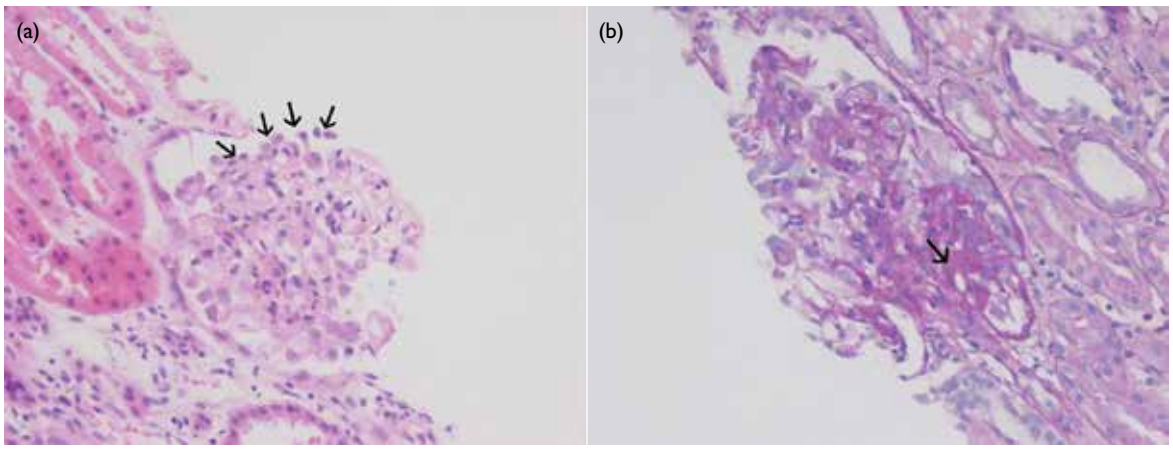

FIG 1. Case 1. Renal biopsy findings showing (a) a haematoxylin and eosin stain of a glomerulus with segmental podocyte hyperplasia (arrows) causing segmental collapse on the underlying capillary lumen (×200) and (b) periodic acid–Schiff stain revealing a segmental collapse (arrow) in the glomerular capillary walls with podocyte hyperplasia (×200)

rituximab treatment. Additionally, he received albumin infusions, diuretics, and antihypertensives. Since the clinical features and laboratory parameters did not improve, the patient underwent plasma exchange. After two sessions, haemodialysis was required due to worsening symptoms, uncontrolled hypervolaemia, and renal failure. No additional immunosuppressive was given at that time and the patient continued to receive haemodialysis. Genetic testing for mutations of the *NPHS1* and *NPHS2* genes were negative.

Case 2

Another 17-year-old male was admitted to our institution in February 2016 for syncope. He had a history of headaches with intermittent vomiting for the previous 2 months and had been treated with metamizole, domperidone, zolmitriptan, and diclofenac. His mother had a history of minimal change disease aged 6 years. The patient's blood pressure was measured as 200/120 mm Hg, and hypertensive retinopathy was observed during the ophthalmological examination. Initial serum creatinine level was 4.7 mg/dL and serum albumin level was 3.4 g/dL. Ferritin and parathyroid hormone levels were 274 ng/mL and 220 pg/mL, respectively. Microscopic urinalysis showed eight red blood cells per high-power field. He had nephrotic proteinuria of 3820 mg/day (91.5 mg/m^2/h). Viral serology and autoimmune tests (antinuclear antibodies, anti–double-stranded DNA antibodies, anti–glomerular basal membrane antibodies, and anti-neutrophil cytoplasmic antibodies) were negative and complement levels were normal. Abdominal ultrasound revealed increased renal echogenicity. Cranial magnetic resonance imaging showed signs of posterior reversible encephalopathy syndrome. Hypertension was controlled using intravenous and oral antihypertensives (esmolol, captopril, amlodipine, doxazosin, and minoxidil). On the fourth day, the serum creatinine level increased to 5.9 mg/dL and the albumin level decreased to 2.4 g/dL. Kidney biopsy showed severe CG (Fig 2). Because the findings were chronic, no steroids or other immunosuppressive treatment were administered. Genetic testing for mutations of the *NPHS1* and *NPHS2* genes was negative. By the fifth month, the patient's serum creatinine level had reached 6.9 mg/dL. After 1 year of peritoneal dialysis, he received a renal transplant.

Discussion

Collapsing glomerulopathy is a histopathological pattern of podocytopathies.[1] It was previously classified as a variant of focal segmental glomerulosclerosis (FSGS), known as collapsing FSGS.[2-4] However, it is more severe at the initial stage and progresses more rapidly to end-stage kidney disease compared with non-collapsing FSGS, even when treatment is given.[2-5] It typically presents with nephrotic proteinuria and elevated serum creatinine level, and is rare among children.[3,5]

Both patients had high serum creatinine level, nephrotic proteinuria, and hypertension. To establish the exact diagnosis and determine the prognosis, a kidney biopsy was performed as the gold standard for diagnosis. Histopathological findings of CG include glomerular capillary collapse in at least one glomerulus; hyperplasia and hypertrophy of visceral epithelial cells leading to pseudo-crescent formation; presence of periodic acid–Schiff-positive hyaline droplets in visceral epithelial cell cytoplasm; and severe tubulointerstitial inflammation in the early stages. Glomerulosclerosis and interstitial

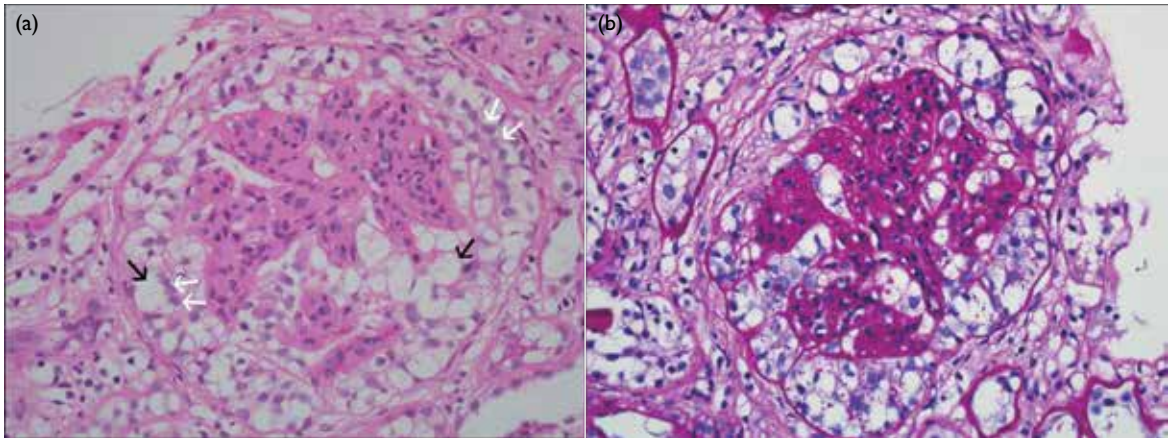

FIG 2. Case 2. Renal biopsy findings showing (a) global glomerular collapse with pronounced podocyte hyperplasia (white arrows) filling the Bowman's space in the form of pseudo-crescent formation (black arrows) [haematoxylin and eosin stain, ×400] and (b) the same glomerulus with periodic acid–Schiff stain (×400)

fibrosis are observed in the late stages, and immunofluorescence assay is typically negative.[1-4,6] Kidney biopsies in both cases showed advanced CG with global glomerulosclerosis and interstitial fibrosis (Figs 1 and 2).

Collapsing glomerulopathy can be either idiopathic (primary), genetic (familial), or reactive (secondary).[1] The idiopathic form is characterised by the loss of maturity markers and the re-expression of immaturity markers leading to the proliferation of immature podocytes.[1] Secondary causes of CG include infections (human immunodeficiency virus, parvovirus B19, cytomegalovirus, hepatitis C virus, severe acute respiratory syndrome coronavirus 2), drugs (including valproic acid and anabolic steroids), autoimmune diseases (such as systemic lupus erythematosus), and malignancies.[1-4,7] Genetic CG is associated with mitochondrial dysfunction that causes podocyte proliferation.[1] Case 1 had a history of long-term use of antiepileptic drugs (phenobarbital, valproic acid, and carbamazepine). However, we found no other aetiological factors in either patient. Therefore, we concluded that while the aetiology in Case 1 could be idiopathic or valproic acid–related, it was idiopathic in Case 2.

There is no specific treatment for CG2; as such, the mainstay of therapy is for the disorders resulting from nephrotic syndrome (such as hypertension and oedema), treatment of the underlying conditions (such as infections and autoimmune diseases), and immunosuppressive therapy.[8] Possible factors for progression to end-stage kidney disease in CG include a serum creatinine level >2 mg/dL at the time of biopsy, proteinuria >8 g/day and lack of remission, collapsing lesions in >20% of glomeruli, and the severe tubular changes and interstitial fibrosis.[3,9,10] In Case 1, the rationale for aggressive immunosuppressive treatment was based on an initial serum creatinine level of 1.6 mg/dL, intense polymorphonuclear leukocytes and eosinophil infiltration, and 2 out of 24 glomeruli showing glomerulosclerosis. Case 2 did not receive immunosuppressive treatment due to the chronicity of the disease and advanced global glomerulosclerosis (67%). The Table summarises the clinical findings in both patients.

TABLE. Initial findings and clinical course of both patients

	Case 1	Case 2
Initial serum creatinine level, mg/dL	1.85	4.7
Initial proteinuria, g/d	6.8	3.8
Histopathological findings		
Collapsing glomerulus	4/24 (17%)	3/15 (20%)
Global glomerulosclerosis	2/24 (8%)	10/15 (67%)
Tubulointerstitial inflammation	Yes (with PMNL and eosinophils)	Yes (with MNC)
Interstitial fibrosis	Yes	Yes
Aetiology	Idiopathic or VPA-related	Idiopathic
Treatment	Supportive treatment Steroid, MMF, rituximab	Supportive treatment
Time from onset to ESKD	2 months	5 months

Abbreviations: ESKD = end-stage kidney disease; MMF = mycophenolate mofetil; MNC = mononuclear cell; PMNL = polymorphonuclear leukocytes; VPA = valproic acid

Conclusion

It is important to recognise that CG is a separate clinicopathological entity from FSGS. Due to the poor response to immunosuppressive drugs and the potential for renal transplantation, we recommend avoiding aggressive immunosuppressive therapy for patients with poor prognostic factors at the time of diagnosis. This approach helps minimise the side-effects of cumulative immunosuppression.

Author contributions

Concept or design: All authors.
Acquisition of data: All authors.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: Y Özdemir Atikel, SA Bakkaloğlu.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

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Ethics approval

Both patients were treated in accordance with the Declaration of Helsinki. Written informed consent for publication was obtained from both patients and their parents.

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