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Case Report

Collapsing Glomerulopathy in a Patient with a TRPC6 Mutation Presenting as Rapidly Progressive Glomerulonephritis: A Case Report and Review of the Literature

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ABSTRACT. Collapsing glomerulopathy (CG) is a proliferative disease characterized by segmental or global wrinkling of the glomerular basement membrane and the formation of pseudocrescents, whereas focal segmental glomerulosclerosis (FSGS) is characterized by podocytopenia, and focal and segmental sclerosis of the glomeruli. Mutations in *NPHS1*, *NPHS2*, *WT1*, *PLCE1*, *CD2AP*, *ACTN4*, and *TRPC6* have been reported in steroid-resistant FSGS patients. The mutations p.R895C and p.R895L in Exon 13 are the only ones in *TRPC6* causing CG reported to date. Here, we present the case of a 17-year-old male patient with a collapsing variant of familial FSGS caused by a mutation in *TRPC6* (p.R895C) who presented with rapidly progressive (crescentic) and proliferative glomerulonephritis.

Introduction

Focal segmental glomerulosclerosis (FSGS) is the second-most common cause of nephrotic syndrome in children. Collapsing glomerulopathy (CG) may be considered a variant of FSGS. CG is a proliferative disease characterized by segmental or global wrinkling of the glomerular basement membrane and the formation of pseudocrescents, whereas FSGS is characterized by podocytopenia, and focal and segmental sclerosis of the glomeruli. It is characterized clinically by heavy proteinuria, progressive renal insufficiency, and rapid deterioration to end-stage renal disease (ESRD). Mutations in *NPHS1*, *NPHS2*, *WT1*, *PLCE1*, *CD2AP*, *ACTN4*, and *TRPC6* have been reported in steroid-resistant FSGS patients. Here, we present a case of CG with a p.R895C mutation, which is one of the two mutations in *TRPC6* causing CG reported to date.

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Case Report

A 17-year-old male patient was admitted to our outpatient clinic with elevated renal function tests and generalized edema. It was

learned that the patient had been followed up for proteinuria in another center for 8 months but did not attend regular follow-up visits. His family history revealed that his father had been followed for 10 years with a diagnosis of FSGS. The father is still being followed up for ESRD and is on the waiting list for cadaveric renal transplantation. Our patient had no risk of human immunodeficiency virus (HIV) infection in his history. He was 178 cm (50–75th percentile) and 62 kg (25th percentile). His physical examination revealed periorbital and pretibial edema, his blood pressure was 140/90 mm Hg, and the other systematic examinations revealed normal results. A laboratory evaluation showed elevated renal function tests (blood urea nitrogen: 33 mg/dL; creatinine: 3.95 mg/dL), hypoalbuminemia (albumin: 2.3 g/dL), hyperlipidemia (total cholesterol: 286 mg/dL; low-density lipoprotein: 177 mg/dL; triglycerides: 303 mg/dL). His 24-h protein excretion was 17.9 g/day. The serological, antinuclear antibody, and antineutrophilic cytoplasmic antibody tests were negative but complements C3 and C4 were normal. The serological workup for viral infections was as follows: anti-Hbs Ag was positive, but Hbs Ag, anti-HIV, and anti-hepatitis C virus were negative. Renal ultrasonography revealed normal-sized kidneys for his age and height and increased parenchymal echogenicity.

A percutaneous kidney biopsy was performed. In the first evaluation, light microscopy demonstrated the formation of crescents in 13 out of 18 glomeruli (Figure 1). When we reevaluated these lesions with our pathologist after the results of the genetic testing became available, we interpreted them as collapsed glomerular tufts associated with pseudocrescents and the proliferation of visceral epithelial cells. There was interstitial fibrosis and tubular atrophy in multiple areas but no mesangial hypercellularity and expansion. Direct immunofluorescence showed negative staining. Electron microscopy revealed significant obliteration of the podocytes. Despite negative immunofluorescence staining, the patient was first evaluated as having rapidly progressive glomerulonephritis because of the presence of crescents revealed by light microscopy. Because of the histopathological findings detected through the kidney biopsy, pulse methylprednisolone and intravenous cyclophosphamide therapies were initiated. Despite therapy, his creatinine level rapidly increased to 9 mg/dL in 1 month. Plasmapheresis was initiated, but his creatinine levels did not regress. ESRD developed rapidly in this patient, and hemodialysis was initiated.

A heterozygous mutation in *TRPC6* changing a cytosine to a thymine in Exon 13 (c.2683C>T), which substituted an arginine for

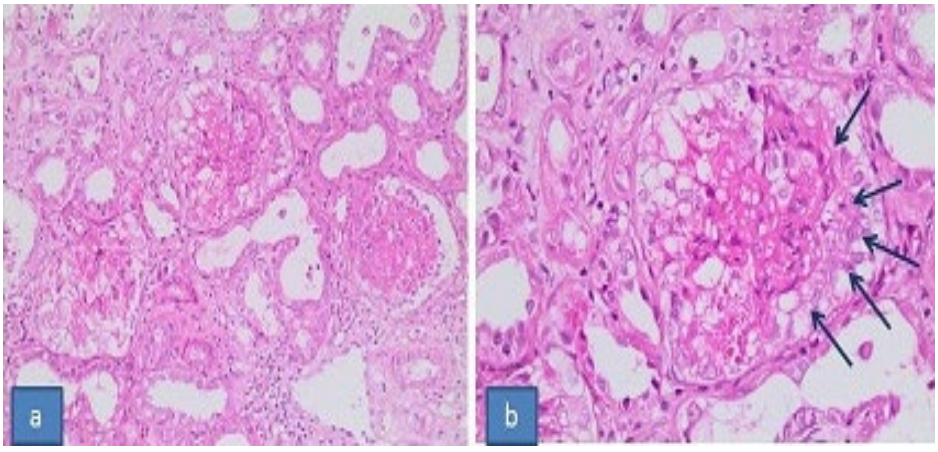

Figure 1. Microscopic view of the kidney biopsy showed that the majority of the glomeruli showed variable degrees of collapse of the glomerular tufts associated with pseudocrescents and proliferation of the visceral epithelial cells (hematoxylin and eosin staining, ×200 and ×400).

a cysteine (p.R895C) was detected in genetic testing. The patient was diagnosed with a collapsing variant of autosomal dominant FSGS with clinicopathological findings in addition to genetic mutation. A living-donor kidney transplantation from his mother was performed 6 months ago, and he is still being followed and has normal renal function.

Informed consent was received from the patient's parents to publish this report.

Discussion

CG was first described by Weiss et al as a podocytopathy characterized by segmental or global collapse of the glomerular tufts, swelling of the podocytes, hyperplasia, tubulocystic changes, and tubulointerstitial inflammation.[1] It is an aggressive variant of FSGS and, as observed in our patient, it is associated with heavy proteinuria, a rapid decrease in the glomerular filtration rate, a lack of response to immunosuppressive drugs, and a poor prognosis.

Examinations of the light microscopy slide of the renal biopsy specimens of patients with the collapsing variant of FSGS demonstrate segmental or global collapse of the glomerular tufts and visceral epithelial hyperplasia and hypertrophy, which can be interpreted as a pseudocrescent, as in our patient. However, crescentic glomerulonephritis has parietal epithelial proliferation. Immunofluorescence microscopy generally shows no deposition. In the electron microscopy images, the glomerular basement membrane was wrinkled and collapsed. The overlying visceral epithelial cells show hypertrophy and hyperplasia, with frequent vacuoles and protein droplets. There was extensive foot process effacement and no or limited mesangial deposits.[2] Misinterpretation of the visceral epithelial proliferation around the collapsing segments as a crescent is possible, and this may result in misdiagnosis of crescentic glomerulonephritis, especially in cases with extensive collapsing sclerosis. There are some morphologic clues that differentiate collapsing sclerosis and a true crescent. The central location of the visceral proliferation, and the presence of a space between the visceral proliferation and the parietal epithelial cells of the Bowman space favor a pseudocrescent (Figure 1), whereas the presence of a rupture of the basement membrane and the presence of fibrin within the Bowman space favors a true crescent. The cytoplasmic vacuolization of the visceral epithelial cells is also another clue that can be used for a diagnosis (Figure 1).

CG is generally classified as idiopathic with underlying genetic mutations, and as a secondary disease that is often related to HIV infection, hepatitis C, human T-lymphotropic virus type 1, parvovirus B19, and loa filariasis. Renal vascular ischemia, systemic lupus erythematosus, drugs (pamidronate, interferon, anabolic steroids, and heroin, etc.), and hematologic neoplasia are other causes of secondary CG.[3-11] CG is sometimes associated with rare syndromes such as action myoclonus–renal failure, mandibuloacral dysplasia, or *WT1*-gene-associated syndromes.[12] A deficiency in the primary coenzyme Q10 has also been described as a cause of CG.[13]

Mutations in *NPHS2*, *TRPC6*, *CD2AP*, and *PLCE1* have all been incriminated in genetic forms of FSGS but not of the collapsing type. Mutations in *ACTN4* and the human Apolipoprotein L1 encoded by the *APOL1* gene have been associated with CG. Since 2005, hetero-zygous mutations of *TRPC6* have been iden-tified as the cause of late-onset autosomal dominant FSGS.[14-18] In 2011, Gigante et al[19] and Liakopoulos et al[20] demonstrated new mutations in Exon 13 of *TRPC6* in 2-year-old girl years and a 21-year-old woman, respectively, with CG. Gigante et al[19] analyzed *TRPC6* in 33 Italian children with sporadic early-onset steroid-resistant nephrotic syndrome (SRNS) and three Italian families with adult-onset FSGS. They demonstrated that variants of *TRPC6* could also be detected in children with early-onset and sporadic SRNS, and they reported a *de novo* mutation of *TRPC6*, p.R895L (c.2684G>T), in a 2-year-old girl with CG. Liakopoulos et al[20] reported a family with multiple members who had CG. Genetic analysis of this family revealed a p.R895C

(c.2683C>T) mutation in *TRPC6*, as in our patient. This is the third study demonstrating that CG is caused by a mutation in *TRPC6*. Unfortunately, we do not know if the p.R895C mutation in our patient is *de novo* or not because we were not able to perform a mutational analysis of his father, in whom the progression of the disease and the renal pathologies, which were performed twice at an interval of 5 years, were not compatible with the collapsing variant of FSGS. To the best of our knowledge, as of 2011, no other mutation in *TRPC6* has been demonstrated to cause CG, except p.R895L and p.R895C.

The *TRPC6* gene is located at the long arm of chromosome 11 (11q22.1) and codes for the transient receptor potential cation channel, Subfamily C, Member 6.[19] It drives the influx of calcium into the cell. *TRPC6* is expressed in the renal tubules and glomeruli, especially in the podocytes. So far, about 30 different mutations causing FSGS (nearly 40% of these mutations occur in Exon 2 and 19% in Exon 13) have been reported in *TRPC6*, of which only two have been associated with CG.[19-21] p.R895C is a gain-of-function mutation and a non-tolerated change that affects the protein's function, causing increased TRPC6 activity. In contrast, p.R895L is a loss-of-function mutation resulting in reduced basal channel activity. Both mutations were shown to be located on Exon 13 of *TRPC6* and are very close to each other. This region in Exon 13 seems to act as a hot spot of mutations causing CG.

In summary, we should suspect the collapsing variant of FSGS, especially in patients with a progressive clinical course and a renal pathology similar to rapidly progressive glomerulonephritis who have a poor response to empirical immunosuppressive therapy and exhibit a rapid deterioration in renal function. It should also be kept in mind that p.R895L and p.R895C mutations in Exon 13 of *TRPC6* have a strong association with the collapsing variant of FSGS.

Conflict of interest: None declared.

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