Case Report

Clinicopathological Implications of Proteinuria after Long-Term Isolated Hematuria due to Thin Basement Membrane Nephropathy and Focal Segmental Glomerulosclerosis

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1. Introduction

The common causes of isolated microscopic hematuria among children and young adults are IgA nephropathy, thin basement membrane nephropathy (TBMN) and Alport syndrome (AS) [1, 2]. It is well recognized that both IgA nephropathy and AS could develop proteinuria, hypertension and renal dysfunction, resulting in end-stage kidney disease (ESKD). Although the renal outcome was believed to be generally good in TBMN, recent studies showed that a subgroup of TBMN is at increased risk of ESKD due to the late onset of focal segmental glomerulosclerosis (FSGS) [3]. Therefore, patients with persistent isolated microscopic hematuria, whatever the cause among children and young adults, need long-term follow-up to monitor proteinuria, renal function and blood pressure to provide patients with proper treatment at an appropriate timing.

We herein report a 45-year-old obese man who presented with proteinuria after long-term isolated hematuria. Kidney biopsy revealed TBMN and FSGS. We judged that his FSGS was caused by obesity because of its histological features. Differential diagnoses of clinical situations involving co-occurrence of TBMN and FSGS were also discussed.
remarkable. Urinary examination showed proteinuria of 0.7 g/g creatinine, red blood cell of 10-19/high power filed and positive red cell casts. Blood chemistry showed serum creatinine of 0.69 mg/dL, cystatin C of 0.74 mg/L, albumin of 4.1 g/dL, uric acid of 6.3 mg/dL, LDL-cholesterol of 144 mg/dL and HbA1c of 5.5%. The estimated glomerular filtration rate calculated by the revised serum creatinine–based Japanese equation [4] was 97.6 mL/min/1.73 m². Immunological examination indicated no abnormal results including C-reactive protein, IgG, IgA, complement and anti-nuclear antibody. The electrocardiogram and chest X-ray were normal. Abdominal ultrasound detected normal shape and size in the kidneys.

With a clinical suspicion of IgA nephropathy, kidney biopsy was performed. Kidney biopsy revealed 1 global sclerosis out of 16 obtained glomeruli. Nonsclerotic glomeruli exhibited slight enlargement (glomerular diameter from 180 µm to 200 µm) without significant proliferative changes. One glomerulus showed segmental sclerosis at the perihilar region, diagnostic of FSGS (Figures 1(a)–1(c)). There were mild degree of tubular atrophy and interstitial fibrosis accompanied by mononuclear cell infiltration. Mild intimal thickening in small arteries and arteriolar hyalinosis were found. Immunofluorescent study showed no deposition of immnoreactants and a preserved linear alpha-5 of type IV collagen staining (Figure 1(d)), supportive for TBMN rather than AS [5]. Electron microscopy showed thinning of the glomerular basement membrane (GBM) (GBM width between 140 nm and 250 nm) without splitting or lamellation, fulfilling the diagnostic criteria of TBMN (Figure 2) [5]. Foot process effacement was partial, and glomerular epithelial detachment was not seen (Figure 2). Hypertension can be a cause of FSGS [6]. However, it is less likely that FSGS lesion in our patient was caused by hypertension because that his hypertension was less severe degree and that kidney biopsy did not include ischemic glomerular lesions, which are a common feature in hypertensive nephrosclerosis [7].

Reduction of body weight by diet therapy from 98.7 kg to 92.0 kg, and increasing a dose of angiotensin-receptor blocker, losartan potassium to 100 mg/day successfully reduced blood pressure to 125/75 mmHg and proteinuria from 1.16 to 0.16 g/g creatinine 9 months after the kidney biopsy. However, subsequently re-increase in body weight brought about increasing proteinuria up to 1.2 g/g creatinine. Microscopic hematuria persisted, and renal function was stable during the clinical course.

3. Discussion

IgA nephropathy, TBMN and AS, all of three conditions can present with the manifestations of proteinuria after short or long-term isolated hematuria [1, 2]. Our patient with
podocytopathy, such as diffuse process effacement and our FSGS was a secondary lesion because strong evidence of abnormalities. Histopathologically, however, we believe that we were unable to determine if FSGS was caused by genetic factors. As our patient did not undergo genetic analysis, renal outcomes through regular monitoring and early treatment of all disorders arising from abnormalities of the collagen IV might explain about 40% of familial microscopic hematuria due to TBMN [12]. Although the renal outcome was believed to be generally good, it is now recognized that up to 20–30% of patients of familial and sporadic TBMN cases with carriers of heterozygous COL4A3/COL4A4 mutations may progress to the ESKD due to late-onset FSGS often with nonnephrotic proteinuria [3, 12–14] or due to possible subset of AS [15]. Interestingly certain hypomorph podocin variants may act as adverse genetic modifiers predisposing to FSGS when co-inherited with COL4A3 or COL4A4 mutations [16, 17]. No genotype-phenotype correlation was observed [18]. AS and TBMN have a common molecular basis. These conditions arise as a result of mutations in genes COL4A3, COL4A4 and COL4A5 that affect the synthesis, assembly, deposition or function of the collagen IV α345 molecules. Recently, the Alport Syndrome Classification Working Group proposed the classification of all disorders arising from abnormalities of the collagen IV α345 molecules as forms of AS with the goal of improving renal outcomes through regular monitoring and early treatment [19]. As our patient did not undergo genetic analysis, we were unable to determine if FSGS was caused by genetic abnormalities. Histopathologically, however, we believe that our FSGS was a secondary lesion because strong evidence of podocytopathy, such as diffuse process effacement and glomerular epithelial detachment, was absent by electron microscopic analysis.

Next, out of various factors leading to secondary FSGS, obesity was more likely to be the main cause because of our patient’s morbid obesity. ORG is usually defined as glomerulomegaly with or without perihilar segmental glomerular sclerosis and partial foot process effacement in patients with BMI ≥30 kg/m² [8]. Typically ORG presents with either subnephrotic or less commonly nephrotic range proteinuria [8]. A glomerulomegaly with perihilar FSGS and relatively mild foot process effacement with moderate proteinuria can help to diagnose obesity-associated FSGS in our patient. However, it may not be easy to distinguish secondary FSGS from primary one from morphological aspects especially in the early phase of disease without any risk factors for secondary FSGS. As reported [8], reduction of body weight and reinforcement of renin angiotensin system inhibition were effective on reduction of proteinuria in our patient. This also supported a dual diagnosis of TBMN and obesity-associated FSGS.

TBMN is not a rare disease since about 1% of the population is affected [20]. However, there is no evidence that TBMN alters the prognosis of another glomerulopathy [21]. On the other hand, obesity seems to worsen the renopathological state in chronic kidney disease [8, 22]. It is largely unknown whether obesity-associated FSGS or hypertension-associated FSGS is easy to develop in patients with TBMN. Given that the incidence of obesity and ORG has been increasing worldwide, we predict that more cases with a dual diagnosis of TBMN and obesity-associated FSGS might be reported in the future [8, 23].

In summary, we experienced a patient with proteinuria after long-term isolated hematuria, diagnosed as TBMN complicated by secondary FSGS associated with obesity. Analysis of COL4A3 or COL4A4 mutations might be helpful to know the underlying risk not only for FSGS but also for AS in patients with long-term isolated hematuria [3, 15]. However, genetic diagnosis that can predict a progression of FSGS in patients with TBMN has not been established, therefore careful evaluation of clinicopathological findings is essential for a proper diagnosis and an appropriate treatment.

Additional Points

This article does not contain any studies with human participants performed by any of the authors.

Consent

Written informed consent was obtained from the patient.

Conflicts of Interest

The authors have declared that no conflict of interest exists.

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