EXCEPTIONAL CASE

Tissue is the issue: when a second biopsy reveals the true diagnosis

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ABSTRACT

We describe the case of a woman with minimal glomerular changes on initial kidney biopsy. On long-term follow-up, the patient developed nephrotic proteinuria and a second kidney biopsy was performed, which revealed focal segmental glomerulosclerosis (FSGS). Findings from electron microscopy (EM) examination suggested a genetic form of FSGS. Next-generation sequencing showed heterozygosity for a mutation in COL4A3. Collagen IV nephropathies can be linked to late-onset FSGS. By establishing a genetic cause of FSGS, immunosuppressive treatment can be avoided. This case emphasizes the importance of re-biopsy in cases of a non-explained rise in proteinuria. EM can be helpful in differentiating between primary and secondary FSGS and informing treatment strategies. In cases of adult-onset FSGS that cannot be categorized by clinical–pathological assessment, genetic testing should be considered.

Keywords: collagen IV nephropathies, focal segmental glomerulosclerosis, gene expression, glomerulonephritis

CASE DESCRIPTION

A 41-year-old woman, with a previous history of microscopic haematuria since childhood, was referred for persistent proteinuria that began since January 2006, following a second pregnancy complicated by pre-eclampsia (Supplementary data, Figure S1).

With proteinuria reaching >1 g/24 h, an initial kidney biopsy was performed in December 2007, which showed minimal glomerular changes on light microscopy (LM) examination. Electron microscopy (EM) revealed features of diffuse podocyte foot process effacement (FPE), and no changes were observed in the glomerular basement membrane (GBM) (Figure 1A). A non-immunosuppressive treatment regimen, comprising an angiotensin-converting enzyme inhibitor (ACEi), a statin and a nephroprotective diet, was initiated.

Over the next 10 years following the above treatment, the patient remained clinically stable with no hypertension or oedema. Biochemical parameters were maintained within the normal range, with an estimated glomerular filtration rate of >90 mL/min and proteinuria of <1.5 g/24 h.

At the end of 2017, the patient developed nephrotic-range proteinuria, in the absence of nephrotic syndrome, without any obvious trigger. A second kidney biopsy was performed, and both light microscopy (LM) and immunofluorescence examination revealed characteristic pathological features leading to a diagnosis of focal segmental glomerulosclerosis (FSGS).
On EM examination, there was 100% podocyte FPE, and the GBM showed splitting of the lamina densa (Figure 1B). Foamy cells were seen, which were also observed in the first biopsy (Supplementary data, Figure S2).

Our patient showed no clinical features of Alport syndrome and did not have any family history of kidney disease. However, as lamina densa splitting is diagnostic of Alport syndrome, next-generation sequencing (NGS) was performed (Supplementary data, Table S1), which showed heterozygosity for a pathogenic mutation in the COL4A3 gene. The presence of a heterozygous mutation in COL4A3 is usually associated with an autosomal dominant form of microscopic haematuria. Collagen IV nephropathy shows considerable heterogeneity, and a dominant form of progressive FSGS has been described in some families [1–4].

Immunosuppressive treatment is not appropriate in the management of genetic forms of FSGS, and non-immunosuppressive measures have to be continued life-long. Genetic testing with NGS is recommended in all first-degree relatives of kidney biopsy [5].

Adequate biopsy sampling is essential for tissue detection of FSGS. Furthermore, timing of the biopsy with respect to the disease course is important. The initial pathological changes of podocyte FPE are only detectable by EM, because the characteristic sclerotic lesions take time to develop.

Findings on LM examination are rarely pathognomonic for particular forms of FSGS. The major ultrastructural finding on EM is FPE [3, 5], which can help distinguish between primary and secondary forms of FSGS. Although diffuse FPE is not a defining signature of primary FSGS, it eliminates maladaptive secondary mechanisms as the cause of the FSGS lesions. A genetic form of FSGS must be considered when either diffuse or segmental FPE is observed. EM can help to identify FSGS as a manifestation of the expanding spectrum of collagen IV nephropathies [1–3, 5] by revealing an irregular thickening of the GBM with splitting of the lamina densa.

Collagen IV nephropathies comprise benign familial microscopic haematuria, thin basement membrane nephropathy, X-linked Alport syndrome and also autosomal recessive and dominant Alport syndrome. Apart from the X-linked form of Alport syndrome, which is caused by hemizygous mutations in the COL4A5 gene, the other entities are caused by mutations in the COL4A3 or COL4A4 genes [1–4].

The spectrum of collagen IV nephropathies [1–5] is broad and expanding rapidly and, more recently, has included late-onset FSGS, which develops alongside thin basement membrane nephropathy in later life, as described here. At one end, we find phenotypes of benign familial microscopic haematuria, while intermediate phenotypes are also present and can evolve progressively towards end-stage renal disease in later life.

Deltas et al. [1] and Ars and Torra [4] hypothesize that the full spectrum of phenotypes in heterozygous collagen IV mutation carriers behaves as a multifactorial condition that implicates the primary genes, modifier genes and environmental factors. Such wide phenotypic heterogeneity, when accompanied by incomplete presentation of certain signs and symptoms and sometimes also by a lack of detailed histology, including EM, can lead to misdiagnosis, in turn resulting in possibly ineffective and potentially toxic treatments with immunosuppressive agents [3–5].

Long-term follow-up during the course of ageing is mandatory to reveal the entire phenotypic spectrum, as there is a clear age-dependent penetrance. Most likely progression to FSGS and chronic renal failure will only present in late adult life and mostly after 40 years of age [1, 3, 5].

At the same time, this variable expressivity is evidently influenced by the genetic background of each patient and environmental factors. The mechanisms that underlie the development of FSGS and severe renal failure as a result of inheritance of a heterozygous COL4A4 mutation are largely unknown [1, 4].

It is important to recommend referral for genetic testing for all first-degree relatives of patients who are found to have a COL4A3/A4 mutation [1–3, 5]. In cases of positivity, long-term follow-up and preventive measures are mandatory. Management of proteinuria with ACEis or angiotensin receptor blockers, as well as a nephroprotective diet, can delay disease...
progression and influence renal outcomes [3, 5]. In addition, recognizing that a patient has a genetic form of FSGS will have an impact on selecting of a living-related kidney donor and renal transplantation success. Furthermore, there is a substantially lower risk of recurrence of genetic forms of FSGS following transplantation, compared with primary FSGS [3].

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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