Morphological features of primary focal and segmental glomerulosclerosis

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Abstract. Focal and segmental glomerulosclerosis (FSGS) is one of the most common and non-specific patterns of glomerular injury encountered in human renal biopsies. The primary form can be considered when there is a nephrotic syndrome without other causes. The majority of authors agree that podocytes play a role in the development of segmental glomerulosclerosis. The lesion begins with cell hypertrophy, foot process effacement, cell body attenuation, pseudocyst formation, cytoplasmic overload with reabsorption droplets and finally detachment of the glomerular basement membrane (GBM). When the GBM is denuded, it comes into contact with the parietal epithelium and parietal epithelial cells will attach to the GBM, leading to a synchia and, finally, sclerosis. Along this zone, parietal epithelial cells rest on hyalin material. Occlusion and collapse of a group of capillaries is observed, with inclusion of foam cells and hyalin deposits. The origin of primary FSGS has not yet been elucidated. Genetic, racial and developmental factors, macrophages, viral factors and circulating factors are being explored and give encouraging results.

Key words: focal and segmental glomerulosclerosis; podocytes; cytokines; genetic factors; viral factors; transplantation

Introduction

Focal and segmental glomerulosclerosis (FSGS) is one of the most common and non-specific patterns of glomerular injury encountered in human renal biopsies. Only some cases represent idiopathic FSGS, the primary disease entity associated with nephrotic syndrome.

Diagnosing primary FSGS by biopsy is particularly problematic because no universally accepted morphological or clinical criteria for the diagnosis exist [1,2]. Moreover, several synonyms are employed in the literature such as focal and segmental hyalinosis, focal sclerosis, focal hyalinosis or focal glomerulosclerosis, which lead to confusion in this domain of nephrology.

Description of the ‘classical’ or ‘typical’ lesion

The term ‘focal glomerulosclerosis’ is employed because only some glomeruli are affected. Segmental glomerulosclerosis is considered as a segmental solidification of the glomerular tuft, occurring more often in the perihilar region in continuity with the vascular pole. In the affected areas, the glomerular capillary lumina are obliterated segmentally by relatively acellular matrix material (Figure 1B), often associated with inframembranous hyalinosis, endocapillary foam cells and Bowman’s capsular adhesion. The overlying epithelial cells often appear swollen, and can form a cellular ‘cap’ over the sclerosed segment (Figure 1A). Outside of these segmental lesions, visceral epithelial cells are hypertrophic. Deposits of IgM, C3 and, more variably, C1q frequently are found in these areas (Figure 1E) [3–5].

The majority of authors agree that podocyte modifications play a role in the development of segmental glomerulosclerosis [6–8].

Description and propriety of normal podocytes

The podocyte is a very peculiar cell, corresponding to the visceral epithelial cell of the glomerulus. Chromophilic cytoplasm is abundant and the nucleus is clearly seen. By electron microscopy, the podocyte appears as a polarized cell with a small basal membrane domain in front of the glomerular basement membrane (GBM) and a large apico-lateral domain in front of the urinary space corresponding to 90% of the cellular surface. It contains a main cellular body which divides into large extensions which are also divided into digitiform extensions. Podocytes are attached to the outer aspect of the GBM by their foot processes. Podocyte foot processes have a well developed contractile system consisting of longitudinally arranged microfilament bundles that have been shown to repres-
ent a complete contractile system containing α-actin, α-actinin and myosin. A chain of proteins links the actin filaments to the underlying GBM via cell membrane-associated integrins, thereby firmly attaching foot processes to the underlying GBM (Figure 2). Podocytes express α1β1 and αvβ3 chains of integrins in front of the GBM [9,10]. Moreover, the podocytic apico-lateral surface is covered by a thickened glycocalyx containing a high anionic charge. Podocalyxin is the largest component. The podocytic sole does not contain podocalyxin [11].

The podocyte contains numerous enzymes such as neural endopeptidase and dipeptidase, which may play a role in the degradation of peptides with high biological activity. It has been demonstrated that podocytes synthesize autacoids, endothelin and growth factors [platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor, heparin-binding growth factor, transforming growth factor (TGF), fibroblast growth factor] [8,12]. Podocytes are involved in various glomerular functions including GBM turnover, maintenance of the filtration barrier, regulation of the ultrafiltration coefficient and support of the glomerular tuft.

The GBM represents the strongest structural element...
of the glomerular capillary wall. Podocytes act as a second structure-stabilizing system superimposed on the mesangial cell–GBM system. They are attached to the outer aspect of the GBM by their foot processes.

The podocytes have been well studied in experimental models. With respect to cell proliferation, podocytes occupy a unique position among the resident cell types of the glomerular tuft. During ontogenesis, podocytes lose the ability to divide; thus, podocytes in the adult status represent terminally differentiated cells. Podocytes cannot be replaced, and the only way podocytes can cope with any increasing workload is by cell hypertrophy. Multinucleated cells represent an extreme form of hypertrophy [12–14]. In the human, very little is known about the life span of a podocyte and its proliferative potential. Mitotic cells are very rare on renal biopsies. In vitro, with bFGF, podocytes may multiply.

**Development of so-called ‘focal and segmental glomerulosclerosis’**

Many experimental models have allowed the progression of podocytic lesions to be followed.

When exposed to increased challenge of any kind, podocytes are unable to maintain their normal differentiated phenotype but change in appearance in a fairly stereotyped manner [4–8,15,16]. These changes comprise cell hypertrophy, foot process effacement, cell body attenuation, pseudocyst formation, cytoplasmic overload with reabsorption droplets, and finally, detachment from the GBM. When the GBM is denuded, it comes into contact with the parietal epithelium, and parietal epithelial cells will attach to the GBM, producing a synchie and finally sclerosis. Parietal epithelial cells are found along this zone resting on a hyalin material. Occlusion and collapse of a group of capillaries is observed, with inclusion of foam cells and hyalin deposits. In fact, denuding the GBM is responsible for hyperfiltration, and larger proteins are trapped in the subendothelial space giving this aspect.

Podocyte alterations are reversible but, as soon as the glomerular basement membrane is denuded, lesions are irreversible.

These focal and segmental lesions may have different localizations in a given glomerulus. In adults, the most common localization is at the vascular pole. In children, peripheral lesions are more common. In some cases, the lesions are mixed. There is no clear explanation for these different localizations and they probably depend on ultrafiltration flow [17]. In children, endocapillary proliferation can be observed, but usually it is encountered at the beginning of the disease and is transient [18].

**Some particular forms are recognized as present in idiopathic FSGS**

The Tip lesion is observed at the tubular pole, with aggregation and marked vacuolization of podocytes, adhesion of the GBM to Bowman’s capsule, and swelling and foaming of endocapillary cells (Figure 1C). The evolution is characterized by inframembranous hyalinosis and development of typical segmental sclerosis. The significance of this lesion is controversial [19].

The collapsing variant is characterized by an endocapillary space reduced by implosive retraction, wrinkling of the GBM, swollen visceral epithelial cells, abundance of protein resorption droplets and close resemblance to HIV-associated nephropathy (Figure 1D). This form preferentially affects black patients. They have a severe nephrotic syndrome, progressive renal failure and eventually an increased incidence is observed [20,21].

In human primary FSGN, different situations may favour podocyte alterations and development of the disease [22].

**Genetic, racial and developmental factors**

Black race represents a risk factor for malignant forms of FSGS. Blacks have a larger glomerular volume than
with small placentas and having low birth weights [29]. Col IV [37,38]. This observation is interesting because between birth weight and the susceptibility to develop chains of Col IV which are normally produced by In the future, the hypothesis that there is a relationship

References

The hypothesis is that the podocytes lose their adhesive

Viral factors

A role for viral factors may be proposed. Black patients

Podocytic markers and extracellular matrix modifications in FSGS

The expression of adhesion molecules has been studied. The hypothesis is that the podocytes lose their adhesive phenotype which may result in the detachment of podocytes from the GBM. Some authors have shown that podocytes lose the expression of $\alpha_2$ and $\beta_3$. Their conclusion was that these molecules play a role in the development of FSGS [35].

However, in our experience, we have not seen modifications of integrin expression in early lesions. $\alpha_2$ and $\beta_3$ chains, markers of epithelial cells, are well recognized on podocytes in ‘classical’ FSGS and in the ‘collapsing’ form (Figure 2A and B).

Other works have studied different markers of podocytes such as proliferation markers, synaptopodin, podocalyxin, calla, C3b receptor and WT1. There are modifications of these markers when lesions are sclerotic [36].

Extracellular matrix is synthesized in FSGS. Laminin, fibronectin and the $\alpha_5/\alpha_4$ chain of col IV are detected without heparin sulfate or the $\alpha_5/\alpha_4$ chain of col IV [37,38]. This observation is interesting because the affected podocytes are unable to synthesize $\alpha_5/\alpha_4$ chains of Col IV which are normally produced by podocytes.

Renal transplantation

For 25 years, publications regularly have presented recurrence of nephrotic syndrome very soon after renal transplantation when the initial disease was FSGS, and sometimes after several successive transplantations [39–43]. The incidence is variable according to the series (20–50%). The logical hypothesis is that there is a circulating factor which is responsible for the disease and is persistent after renal transplantation. It has been suggested that this factor alters glomerular permeability to macromolecules [44–47]. This hypothesis is supported by the observation that plamapheresis and plasma protein absorption onto a protein A column often decrease urinary protein excretion, although only transiently, in patients with recurrence of nephrotic syndrome after kidney transplantation [48,49]. This factor could be produced by T lymphocytes. Recently, Savin et al. described a factor which is a non-immunoglobulinic, low cationic molecule. This factor increases glomerular permeability. It has been demonstrated that podocyte injury is obtained with a very low concentration of this cytokine-like factor within minutes of introduction [50,51].

FSGS does not correspond to a unique disease. It is a lesion which can be defined as ‘primary FSGS’ but can be encountered in other situations. Certainly, podocytes represent the target which is at the origin of the lesion. Different factors have been proposed to be responsible for the aggression of the podocyte. The development of the lesions has been well studied in experimental models and in human pathology, but the cause of primary FSGS has not yet been elucidated.

References

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