Nephrol Dial Transplant (1999) 14 [Suppl 3]: 58–67

Nephrology
Dialysis
Transplantation

Secondary focal and segmental glomerulosclerosis

F. Ferrario, M. P. Rastaldi and A. Pasi

Renal Immunopathology Centre, S. Carlo Hospital, Milan, Italy

Introduction

The term 'focal and segmental glomerulosclerosis' (FSGS) has been widely accepted as denoting a particular disease entity that manifests itself clinically by the presence of nephrotic syndrome, microscopic haematuria, hypertension and progressive deterioration of renal function [1]. On the other hand, it is well known that morphological evidence of FSGS is present in a very large spectrum of glomerular and interstitial diseases [2].

In recent years, a great deal of research has been carried out, especially on experimental models, to understand the mechanisms leading to glomerular segmental sclerosis [3,4]. At present, there is general agreement that any type of glomerular injury can damage the glomerular intrinsic cell populations that react to the damage by the activation of several pathways, eventually leading to glomerulosclerosis (Figure 1). For example, it is now well known that primary FSGS is a podocyte disease [5], as has been described extensively in the preceding paper. A circulating factor has been hypothesized as the agent causing the damage to the visceral epithelial cells. In its 'classic' form, the characteristic lesion is a segmental solidification of a glomerular tuft, that usually occurs in the perihilar region [5]. The overlying visceral epithelial cells often appear swollen and can form a cellular 'cape' over the sclerosed segment (Figure 2). By immunohistochemistry, we have found that these damaged epithelial cells acquire positivity for cytokeratins, a marker present in the embryonic podocyte but lost by the mature cell, suggesting that damage could also induce a dedifferentiated phenotype [6].

Following the schema presented in Figure 1, it seems that the final glomerular lesion of focal glomerulosclerosis is morphologically indistinguishable in any disease, independently of the underlying mechanism of glomerular injury. Instead, we are absolutely convinced that it is possible to distinguish morphologically different types of glomerulosclerosis in human biopsies probably due to different pathogenetic–morphogenetic

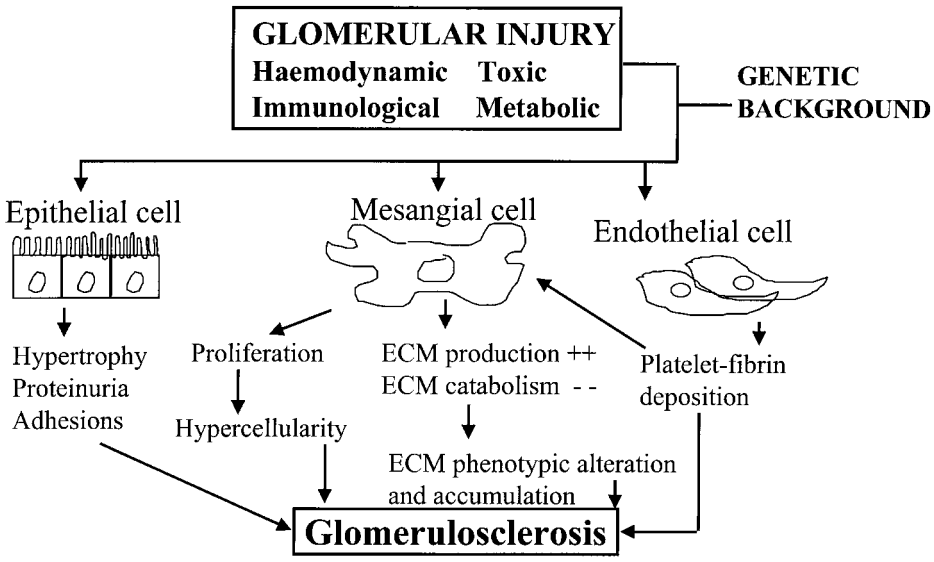

Fig. 1. Pathways leading to focal glomerulosclerosis.

Correspondence and offprint requests to: F. Ferrario, Renal Immunopathology Centre, S. Carlo Hospital, Milan, Italy.

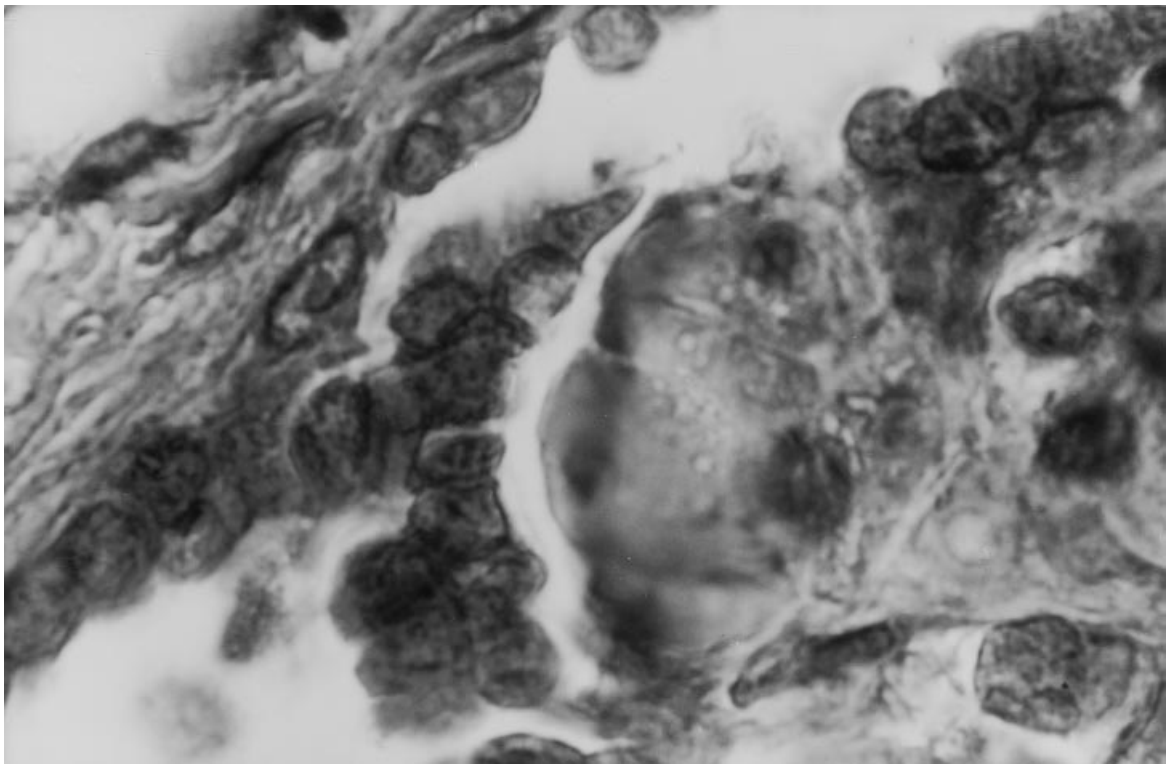

Fig. 2. Primary focal glomerulosclerosis. There is segmental collapse of the glomerular capillaries and an increase in mesangial sclerosis. Glomerular visceral epithelial cells cover or 'cap' the region of segmental sclerosis. (trichrome, $\times 1000$).

mechanisms and that their specific recognition is extremely important in terms of diagnosis, prognosis and therapy, as is discussed here.

Renal vasculitis

A morphological picture of FSGS is present in $\sim 25\%$ of cases of renal vasculitis. By light microscopy, the lesion is peculiar and appears as a well-delineated rounded area, frequently with a clear focal adhesion to Bowman's capsule representing a small fibrous crescent (Figure 3). Sometimes, infiltrating leukocytes with characteristic periglomerular localization are evident. It is well known that active forms of renal vasculitis are characterized by necrotizing extracapillary lesions (Figure 4). By immunofluorescence, the same areas of lesion are positive to fibrinogen antiserum.

Much evidence suggests that segmental sclerosis in renal vasculitis is the consequence of a repair process of a necrotizing lesion. In our experience, this is confirmed not only by repeat biopsies, in which segmental sclerosis has replaced necrosis in the same areas, but also in cases where it is possible to recognize necrotic and sclerotic areas in different glomeruli of the same biopsy (Figure 5) or in the same glomerulus.

We have demonstrated by immunohistochemistry that areas of necrotizing extracapillary lesions contain a large number of monocyte–macrophages and possess an intense staining for the vascular cell adhesion molecule-1 (VCAM-1), a molecule that is completely negative in the normal tuft and that plays a key role in monocyte adhesion [7].

In agreement with many authors, we propose that in renal vasculitis an immunological injury is the cause of a process of capillaritis (Figure 6) [8]. The primary insult is against the endothelial cell that reacts to the damage by platelet and fibrin deposition, cytokine production and expression of adhesion molecules, especially VCAM-1. This causes monocyte adherence and accumulation in the area of lesion. It is known that activated monocyte–macrophages are able to produce many cytokines and growth factors, among which especially transforming growth factor-β (TGF-β) [9] has been demonstrated to play an important role in inducing production of extracellular matrix in order to repair the inflammatory damage. Our immunohistochemical studies have also shown that podocytes surrounding the sclerotic lesions in cases of renal vasculitis are completely negative for cytokeratins, confirming that the mechanism of damage is different from that of primary FSGS [6].

Glomerular sclerosing lesions similar to those of renal vasculitis are detected in cases of Berger's disease and Henoch–Schönlein syndrome. Also in these cases, glomerular segmental sclerosis follows a process of segmental necrotizing extracapillary damage and, in our experience, they also share with renal vasculitis the same immunohistochemical features [10]. Consequently, we argue that the pathogenic mechanism proposed in Figure 6 could also be also applied to this kind of IgA nephropathy.

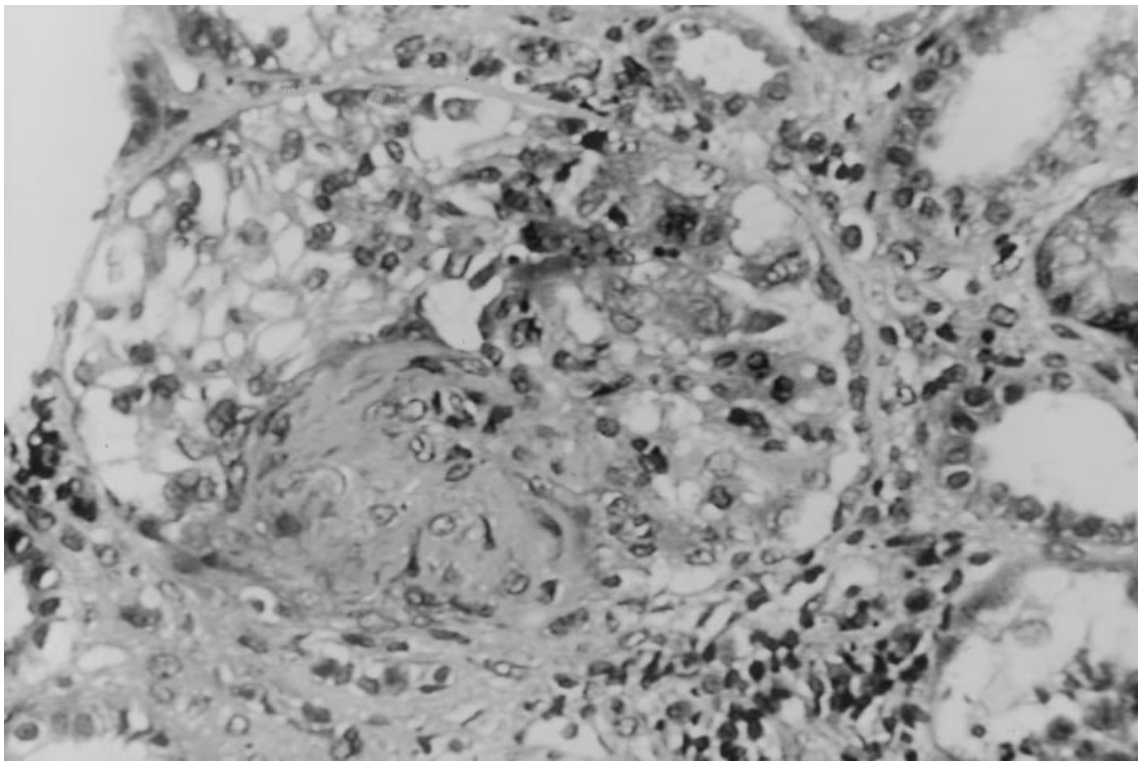

Fig. 3. Microscopic polyarteritis. The glomerulus shows a well-delineated rounded area of glomerulosclerosis, adhesion to Bowman's capsule with the appearance of a small fibrous crescent. Some periglomerular infiltrates are also evident. (trichrome, ×250).

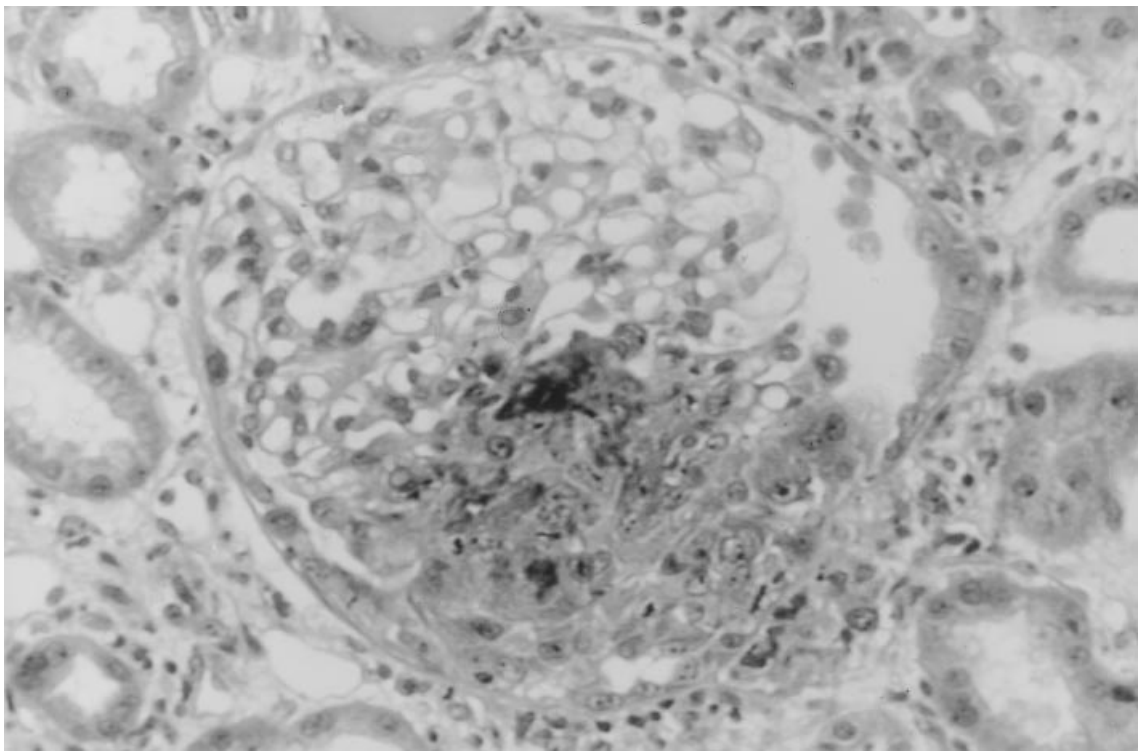

Fig. 4. Microscopic polyarteritis. The typical segmental lesion of tuft necrosis surrounded by crescent formation is evident. The other part of the glomerular tuft is normal (trichrome, ×250).

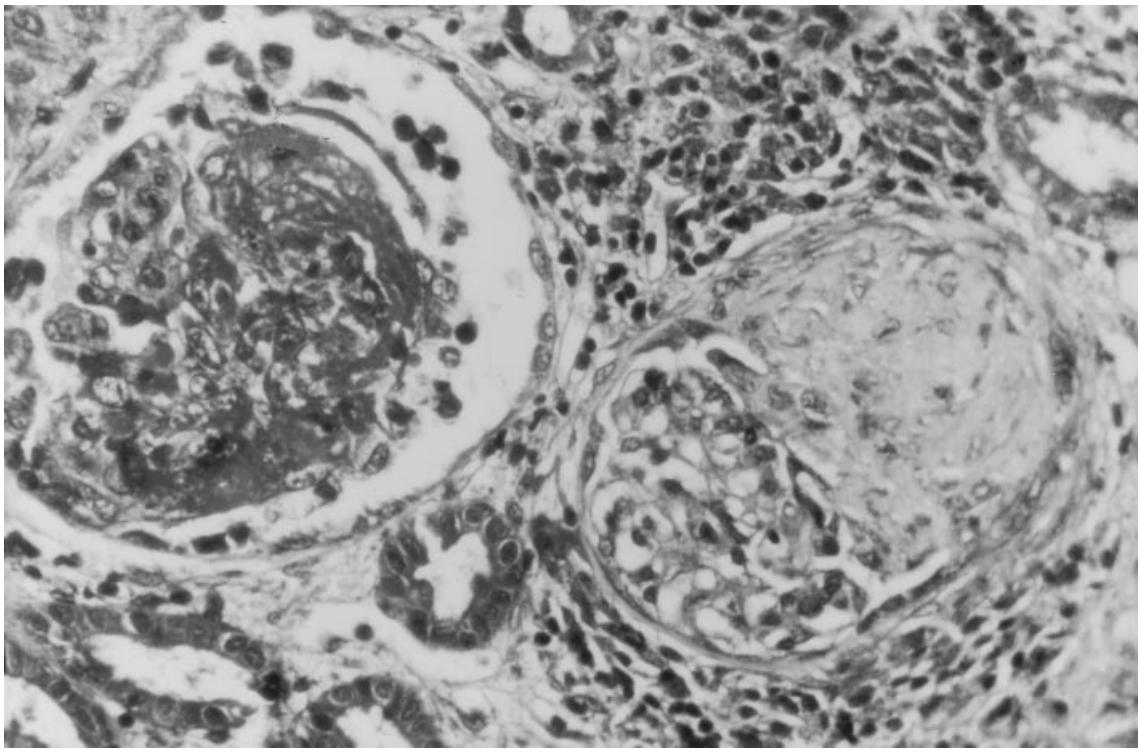

Fig. 5. Wegener's granulomatosis. There is a contemporaneous presence in the same sample of vast intracapillary necrosis (left glomerulus) and a well recognizable segmental area of glomerular sclerosis (right glomerulus). (trichrome, ×250).

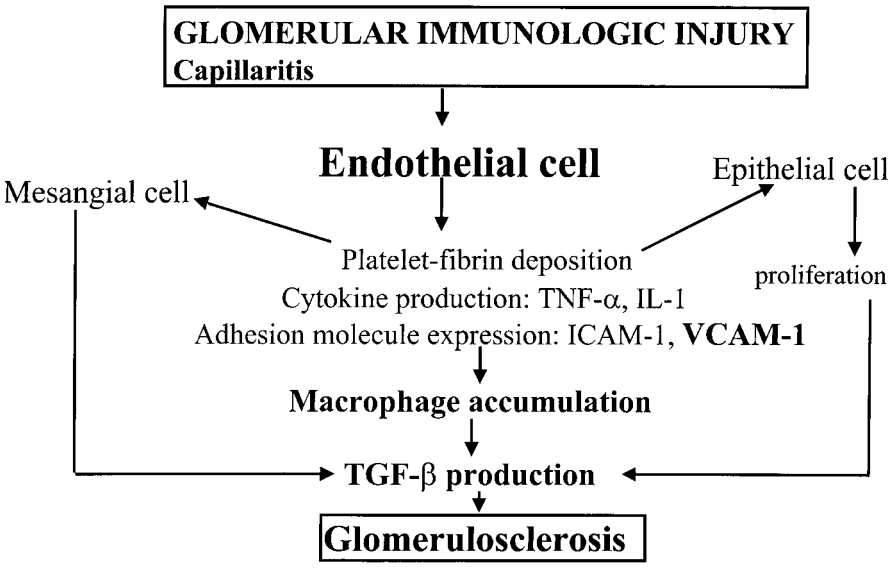

Fig. 6. Pathways leading to focal glomerulosclerosis.

The precise recognition of this type of secondary FSGS is extremely important for the clinico-therapeutical approach for these patients, because repeated formation of necrotizing extracapillary lesions is the major cause of progression of the disease. In our experience, treatment of patients with the necrotizing form of IgA glomerulonephritis has been able to slow progression to end-stage renal failure (Table 1).

Moreover, in the presence of sclerosing lesions at renal biopsy, a correct diagnosis of renal vasculitis, especially in renal limited cases without overt systemic symptoms, prompted us to treat these patients with immunosuppressive drugs and prevented further 'poussées' of capillaritis. These patients had, after 3 years follow-up, a better renal function compared with cases in which the lesion was misdiagnosed and the therapy was not started.

Some cases of lupus nephritis at renal biopsy show

Table 1. Total patients ($n=42$)

	Treated ($n=18$)	Untreated ($n=24$)
Age at renal biopsy (years)	33.6±14.1	32.7±13.3
Interval between onset and renal biopsy (months)	32.2±34	44.9±13.3
Post-renal biopsy follow-up	29.5±24.3	61.1±55.2
Serum creatinine at renal biopsy	1.5±0.5	1.4±0.4
Serum creatinine at follow-up	1.8±0.9 (1 HD)	3.9±3.9 (7 HD)
Proteinuria at renal biopsy	2.3±2.3	2.0±1.1
Proteinuria at follow-up	1.1±0.9	1.6±1.0

peculiar, very rounded and delineated areas of glomerular segmental sclerosis, the remaining part of the tuft being normal (Figure 7). We have demonstrated in six cases, by repeat biopsies, that active proliferative lesions precede sclerosis and that monocytes accumulate in these areas of glomerular damage (Figure 8).

The presence of true intracapillary necrosis is very rare, and a morphogenetic mechanism possibly different from that of vasculitis needs further investigation.

Diabetic nephropathy

Diabetic nephropathy is one of the major long-term complications of diabetes mellitus and its characteristic histological lesion is a glomerular sclerosis of the nodular type, extremely variable in terms of wideness and distribution. In the initial stages of the disease, the number of glomerular sclerotic nodules can be very low (Figure 9), making it difficult to make a correct diagnosis.

The formation of diabetic nodular sclerosis starts from a mesangiolytic process (Figure 10) followed by dilation of the glomerular capillary wall that forms the so-called microaneurysm (Figure 11). As shown in Figure 12, the glomerular injury is caused by metabolic stimuli, such as hyperglycaemia, advanced glycosylation end-products (AGEs) and oxidized low-density lipoprotein (LDL). In the few last years, much evidence from both experimental and clinical studies [11,12], has suggested that AGEs in particular may be responsible for excessive accumulation of extracellular matrix in the glomeruli of diabetic kidneys and thus may play a major role in the pathogenesis of diabetic nephropathy. They are produced by a process involving non-enzymatic modification of tissue proteins by

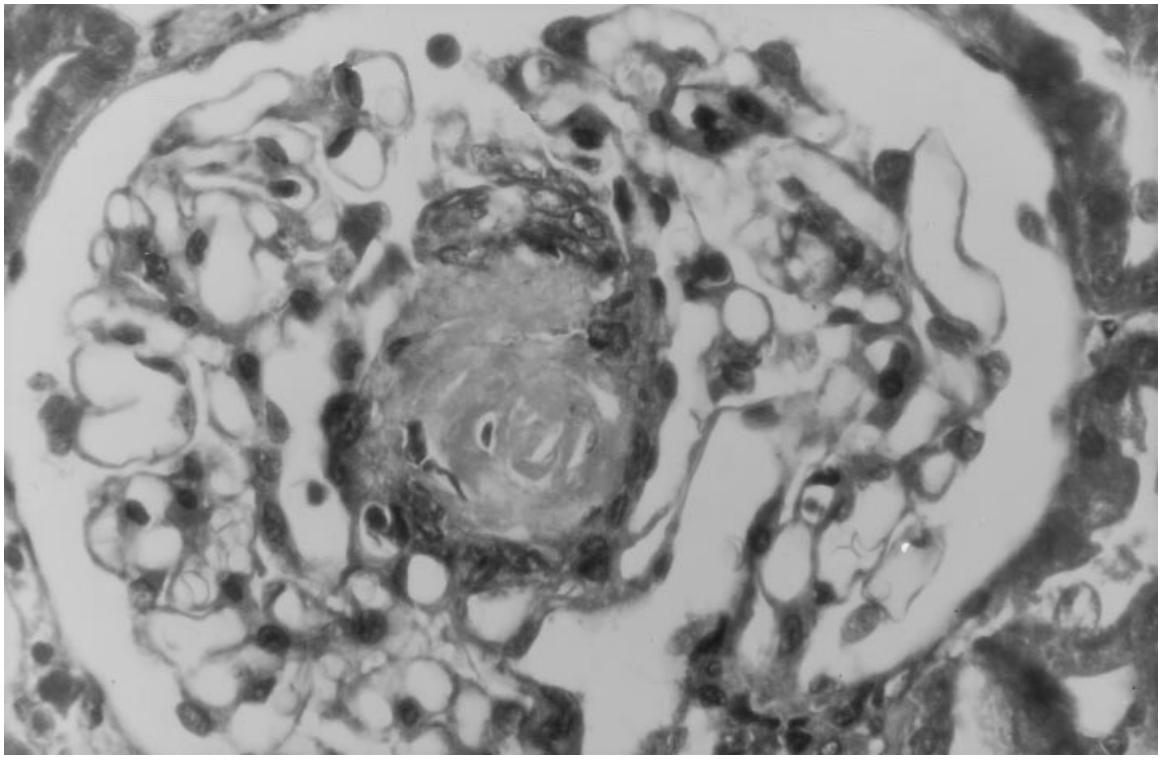

Fig. 7. Lupus nephritis. A peculiar very rounded and delineated area of glomerular segmental sclerosis is evident. The remaining part of the tuft appears quite normal. (trichrome, ×250).

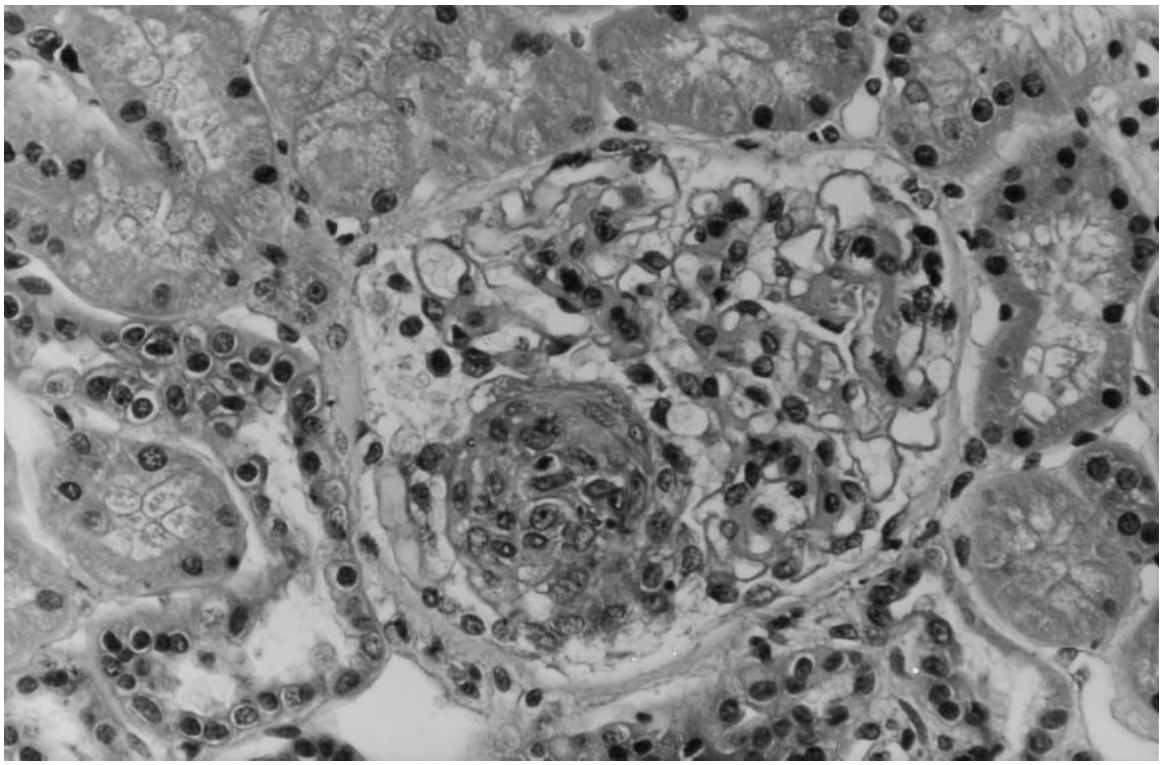

Fig. 8. Lupus nephritis. The glomerulus shows a segmental area of hypercellularity characterized by mesangial proliferation and monocyte accumulation. A clear necrotic lesion of the tuft is not present. (trichrome, $\times 250$).

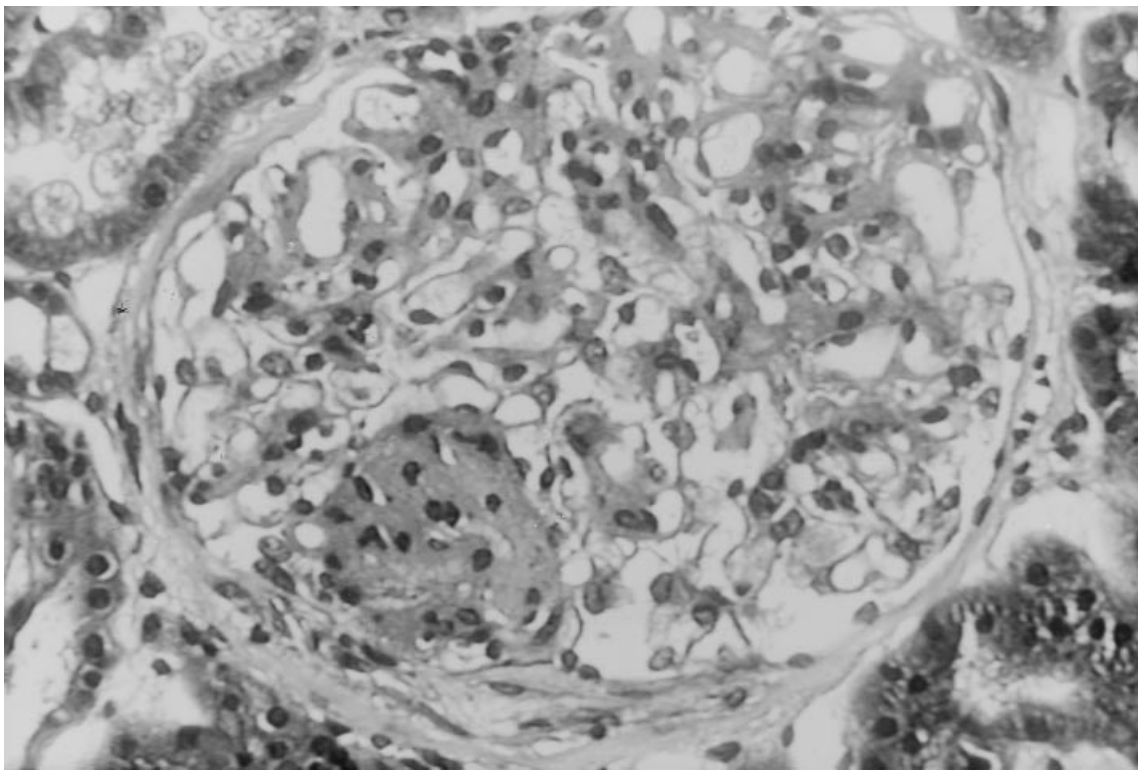

Fig. 9. Diabetic glomerulosclerosis. An isolated small lesion of nodular sclerosis is present. Early stage of diabetic glomerulosclerosis. (trichrome, $\times 250$).

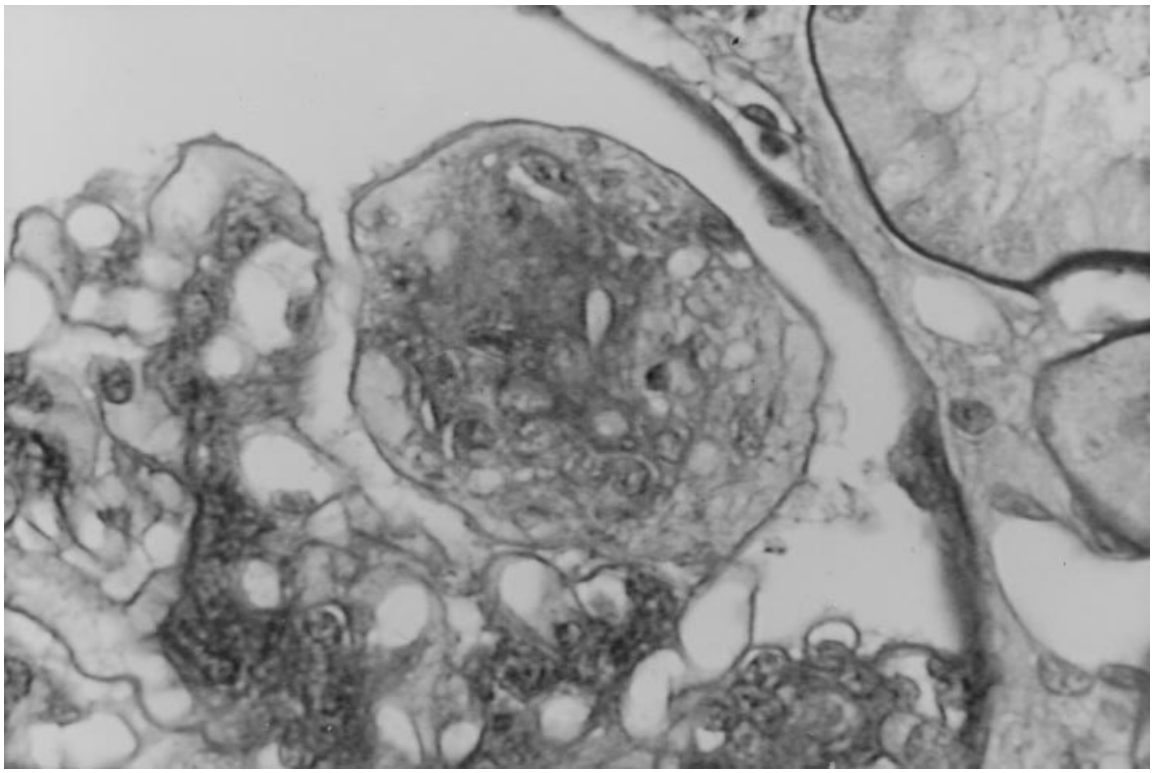

Fig. 10. Diabetic glomerulosclerosis. A mesangiolytic process is evident in a segmental part of the glomerular tuft. (PAS, ×400).

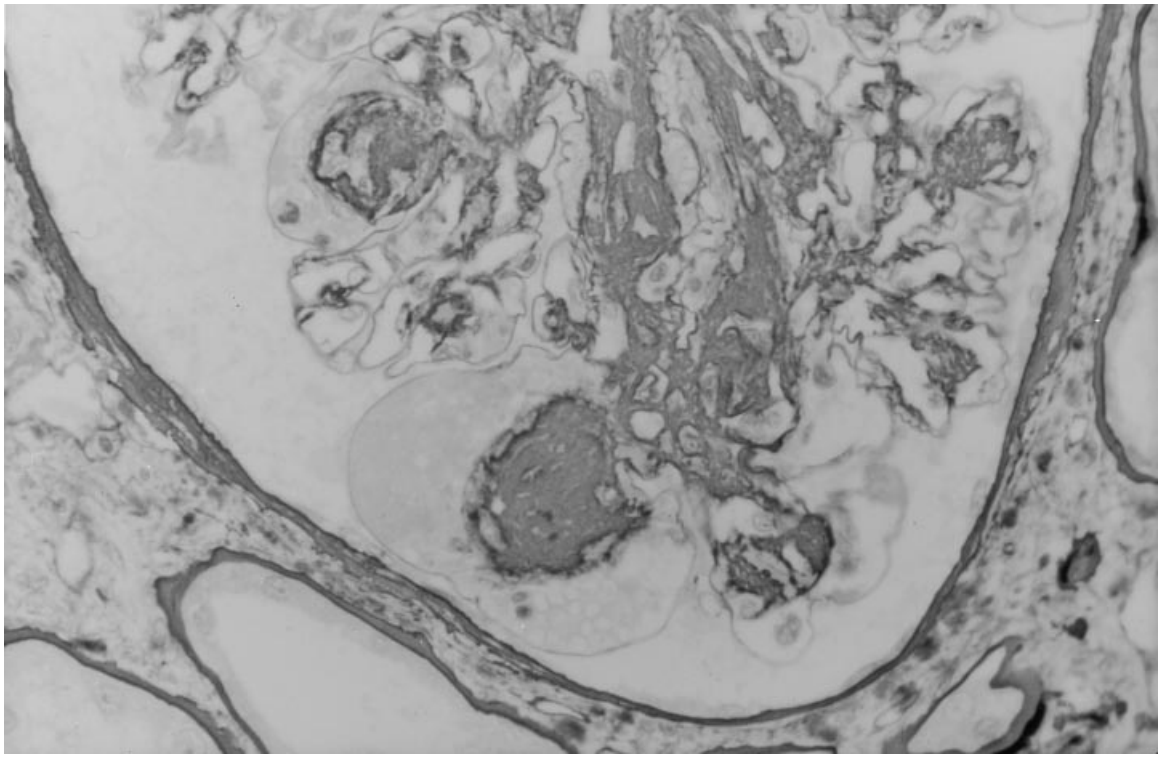

Fig. 11. Diabetic glomerulosclerosis. The detachment of basement membrane from the anchoring point creates a large dilation of the capillary wall forming a typical microaneurysm. In the middle of the microaneurysm, a nodular formation is becoming evident. (silver stain, ×250).

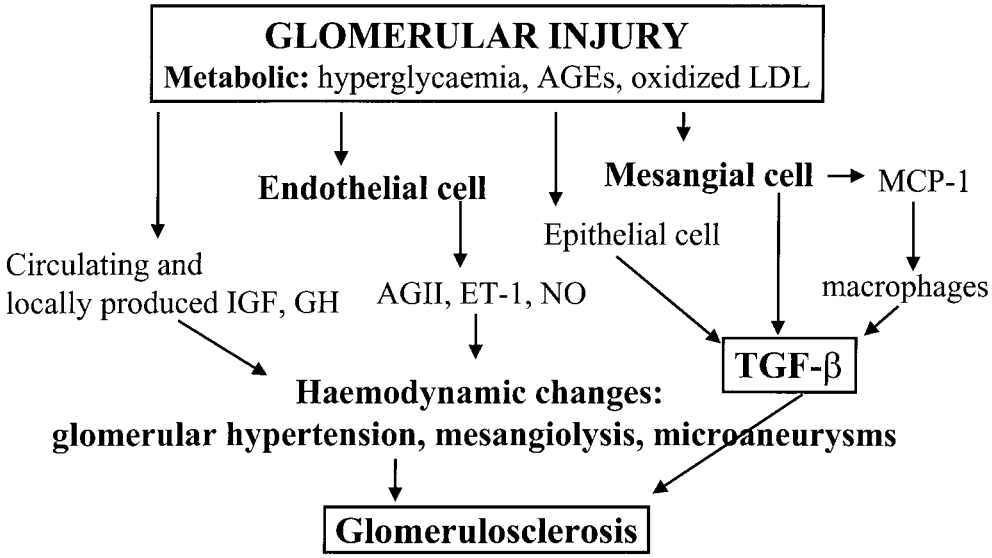

Fig. 12. Pathways leading to focal glomerulosclerosis.

physiological sugars *in vivo*, and accumulate in tissues as a function of time and sugar concentration. Glomerular endothelial cells react to the metabolic damage producing vasoactive factors, such as angiotensin II, endothelin-1 and nitric oxide. All these factors are known to induce haemodynamic changes with the consequent development of glomerular hypertension, mesangiolysis and microaneurysms [13]. Circulating insulin growth factor and growth hormone, overproduced by diabetic subjects, are likely to contribute to the haemodynamic alterations responsible for the induction of glomerular hypertension in this disease [14]. Moreover, the metabolic insults to mesangial and epithelial cells lead to production of cytokines and growth factors, some of them acting as chemoattractants for monocyte–macrophages, others acting in a paracrine manner and activating glomerular cells to proliferate and produce extracellular matrix proteins [15].

In renal biopsies showing a picture of diabetic glomerulosclerosis, we could not find any positivity for cytokeratins in podocytes surrounding the nodular sclerotic lesions, confirming also in this disease a morphogenetic mechanism completely different from that of primary FSGS [6].

A mechanism similar to that inducing diabetic sclerosis, but caused by different stimuli, is likely to operate also in other types of glomerulonephritis characterized by the presence of glomerular nodular sclerotic lesions clearly consequent to the formation of microaneurysms, such as nodular membrano-proliferative glomerulonephritis (both primary and secondary), light chain disease and amyloidosis.

Non-primary focal and segmental glomerulosclerosis

The group of diseases defined as non-primary FSGS comprises the forms (listed in Table 2) that are secondary to structural/functional glomerular adaptations.

Table 2. Non-primary focal and segmental glomerulosclerosis

□	Unilateral renal agenesis
□	Oligomeganephronie and segmental hypoplasia
□	Renal dysplasia
□	Reflux nephropathy
□	Chronic interstitial nephritis
□	Nephrectomy and extensive surgical ablation
□	Morbid obesity

Damage or loss of renal parenchyma initiates most of these diseases, with a critical reduction in the number of functioning nephrons. At renal biopsy, remnant glomeruli are enlarged and show areas of focal segmental glomerulosclerosis. Similar findings are present in patients with either reflux nephropathy or bilateral cortical necrosis or papillary damage secondary to analgesic abuse or sickle cell disease. Likewise, a picture of FSGS at renal biopsy often complicates a congenital deficit of nephron units. Clinically, a mild to moderate proteinuria frequently is seen, but a picture of nephrotic syndrome is rare.

In these diseases, the primary glomerular injury is haemodynamic (Figure 13). It is noteworthy that many of the current concepts on the physiopathological mechanisms underlying FSGS start from experimental models of surgical parenchymal reduction. In these models, one of the central pathological findings is a rapid post-ablation increase in glomerular size, due to increased cell number (hyperplasia) and size (hypertrophy), increased deposition of extracellular matrix and capillary dilation [16]. All of these functional adaptations are caused by the elevated plasma flow rate and the increase in transcapillary hydraulic pressure that increase the single nephron glomerular filtration rate in order to preserve kidney function [17].

As suggested by Floege *et al.* [18], the haemodynamic insult induces a mesangial cell phenotype switch and activation, with expression of α-smooth

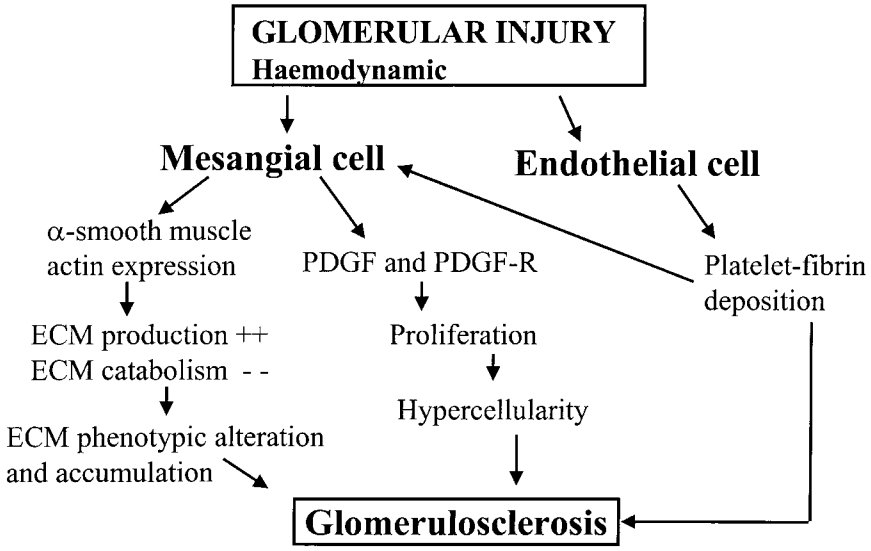

Fig. 13. Pathways leading to focal glomerulosclerosis.

muscle actin. Moreover, endothelial cells are also damaged, with alteration of their antithrombotic properties. These glomerular alterations facilitate deposition and activation of platelets, releasing products that induce mesangial and endothelial cell proliferation, which in turn becomes self-perpetuating by endogenous cytokine production. Secondary to mesangial cell proliferation, matrix overproduction and macrophage influx occur, both of which contribute to the development of glomerular sclerotic changes.

Conclusions

Despite the common definition, secondary forms of FSGS show, in our opinion, very different and clearly recognizable morphological features, probably due to different morphogenetic and pathogenetic mechanisms. We have shown that a correct diagnosis of these different types of glomerular sclerosis is possible and is absolutely relevant for the ensuing clinical and therapeutic implications.

Further studies are required to elucidate better and more precisely the mechanisms involved in the morphogenesis of different types of glomerulosclerosis. Given the diversity of animal models, it is important, in our opinion, that more studies should also be carried out directly on human diseases, to increase our understanding of these forms and lead to more specific therapeutic options.

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