The spectrum of FSGS: does pathology matter?

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The spectrum of podocytropathies ranges from steroid-responsive minimal change disease (MCD) to devastating focal segmental glomerulosclerosis (FSGS), which may recur and cause end-stage renal disease in the transplant. Sclerotic lesions of glomeruli may also develop as a secondary event, both in immune complex and non-immune diseases, such as conditions with extensive loss of renal mass, diabetic nephropathy, arterionephrosclerosis or reflex nephropathy. Even amongst the group of patients with so-called ‘primary FSGS’, there is increasing recognition of a variety of contributing aetiologies, including genetic, viral, drug toxicity and others [1]. Discrimination of clues to patient course and progression could be valuable in stratifying patients according to risk and targeting improved treatment. In addition to the traditional methods afforded by renal biopsy, novel approaches with proteomics, microarray gene expression, genetic influences and others have been used to approach this problem [2–4]. Ultimately, of course, patients do not read textbooks, and we must continue to learn from observations in our patients to further refine and improve our approaches for better understanding of these entities.

In this regard, the studies of Canaud et al. are of interest [5]. They have studied retrospectively a group of 77 patients with idiopathic nephrotic syndrome and ‘FSGS’ in native kidneys who underwent renal transplantation. Of this largely paediatric cohort, 42 patients had development of nephrotic range proteinuria after transplantation. As expected, early biopsies performed in these patients with recurrent nephrotic syndrome showed no lesions by light microscopy in most patients (32/33). One of these early recurrent nephrotic syndrome biopsies showed perihilar variant FSGS. This constellation of lack of sclerosis in a setting of presumed recurrent disease clinically was a condition unfortunately designated as ‘minimal change disease’ by the authors (see below). Over the long-term follow-up, a total of 20 patients had FGS lesions in the transplant, and of these, seven showed collapsing lesions at time points ranging from 6 to 48 months after transplant (on average 22 months). Biopsies done at month 3 in 40 of the patients showed lesions in 14 patients. Of interest, lesions observed in month 3 biopsies were the same as seen later in seven of the eight patients who had segmental lesions at both time points, with one patient showing transition from a tip lesion to a perihilar lesion. Patients who showed the same segmental lesions present at both time points included collapsing (n = 2), cellular (n = 3) and perihilar (n = 2) variants.

It is important in analysing segmental lesions in the transplant to recognize that the transplanted kidney remains, of course, a kidney, and is subject to all injuries that may affect the native kidney. In this report, unfortunately, electron microscopy was not done to assess these lesions. This is important in light of the multiplicity of injury that may result in segmental lesions. Recent studies have demonstrated that secondary segmental sclerotic lesions have subtotal foot process effacement, often <50%, whereas primary FSGS typically has extensive foot process effacement [6,7]. Thus, to completely understand the dynamics of the collapsing and perihilar lesions observed, particularly at late time points after transplant, it would be of great interest to examine the extent of foot process effacement and other concomitant lesions that could suggest e.g. calcineurin inhibitor toxicity as a contributor to the collapsing phenotype.

Our recent survey of transplant lesions demonstrated that recurrence of the disease FSGS in the transplant (diagnosed based on significant proteinuria and extensive foot process effacement, with or without overt segmental sclerosis) was very rare after 2 years, and most recurrent FSGS occurred within the first 6 months after transplantation [8]. Thus, segmental sclerotic lesions at later time points most often represented transplant glomerulopathy evidenced by duplication of glomerular basement membrane and increased lamina rara interna and subtotal foot process effacement by electron microscopy; or calcineurin inhibitor toxicity, often with collapsing features and subtotal foot process effacement, with concomitant arteriolar nodular hyalinosis [9]. New approaches to investigate the aetiology of this spectrum of MCD to FSGS lesions include immunohistochemistry, proteomic and gene array studies. Thus, the group of Kerjaschki has demonstrated that dystroglycan staining is markedly decreased in minimal change disease, while remaining intact in the non-sclerotic areas in FSGS [4]. Proteomic and gene array studies by Kretzler also point to a different pathogenesis of minimal change disease and FSGS [2]. The term ‘minimal change disease’ is typically used for a steroid-responsive disease with extensive foot process effacement that ultimately has good outcome. To use this term for the early phase of recurrent nephrotic syndrome in the transplant in a patient with primary FSGS, evident first by foot process effacement, is not in keeping with this clinicopathological classification. Clearly, the foot process effacement in this setting represents the early phase of recurrent...
FSGS, preceding overt sclerosis, is a process that takes longer to develop. Thus, I would view this situation as similar to the comparison of in situ cancer versus early invasive cancer. Certainly, the former would not be classified as benign; both are malignant processes but at different stages. Clearly, the distinction between minimal change disease and FSGS is an area of controversy, but increasing evidence suggests a divergence early on of these two related podocyte injuries, one leading only to proteinuria and the other typically resulting foot process effacement preceding FSGS lesions in the transplant indeed is distinct from MCD comes from our previous analysis of recurrent FSGS in children. Glomerular hypertrophy is present in patients with extensive foot process effacement without diagnostic segmental sclerotic lesions who ultimately develop overt FSGS, but not in patients with MCD. Glomerular hypertrophy did not occur in children receiving an adult kidney who did not develop FSGS. In contrast, those with recurrence of nephrotic syndrome showed glomerular hypertrophy and extensive foot process effacement that preceded development of the recurrent sclerotic lesions [10].

The further question posed by the study of Canaud et al. is whether renal biopsy information regarding the type of sclerotic lesion can be of use in determining outcomes and prognosis in these groups of patients. This study differs from the previous study by Bajema et al., who found overall great fidelity of histologic variant of recurrent lesions to the native kidney lesions [11]. Several factors may contribute to these differences. Firstly, the population in the current study is largely paediatric, and there may be different contributing mechanisms to disease in the pediatric versus adult patients with FSGS lesions. Secondly, only 20 patients had FSGS lesions in transplants in the current study. Furthermore, many of these biopsies were not fully classified due to the lack of electron microscopy. The late development of some of the lesions raises doubt as to whether they truly are recurrence of original disease or represent other injury pathways. Interestingly, the study documents well the transition of lesions over time in several patients. This has also been previously documented, from the time of the original observation by Hoyer et al., who reported on three cases with recurrence of nephrotic syndrome and evolution to FSGS over time in repeat biopsies [12]. The Columbia kidney classification was based on observations in native kidney biopsies [13]. Several studies have documented a better than usual prognosis in those classified as tip lesion by this approach, compared to worse prognosis of those with collapsing lesions [14–16]. Even better prognosis has been observed by Howie when only pure tip lesion was considered, instead of the slightly expanded definition used by our Columbia classification [17]. Of note, recurrence in the transplant of necessity does not look at the whole spectrum of prognostic possibilities in native kidney FSGS, as only those who reach end-stage are included in the transplant group. As proposed in the Columbia kidney classification, the end-stage default state of segmental lesions is indeed the not-otherwise-specified mixture of various scarring lesions, contrasting with the presumed early and lesser severe lesions of cellular and tip variants [13]. Thus, the repeat biopsies in this study and others clearly show the dynamic range of lesions that can occur over time in the evolution to the end-stage kidney.

Biopsy size is also an important component of assessment of focal lesions. It is estimated that a minimum of 25 glomeruli is necessary to detect a low prevalent lesion [18]. Of even further importance, the biopsy must include the areas affected by the disease process, namely the juxtaglomerular region in cases of FSGS [19]. Elegant analysis by the group of D’Agati has demonstrated that additional sectioning may indeed reveal that cases classified as cellular FSGS on initial examination occasionally show defining tip lesions on deeper levels [15].

Thus, the spectrum of FSGS lesions likely includes dynamics related to time of biopsy, as well as divergence of initial pathogenic insults. The histologic phenotype, thus, gives clues to both stage and type of initial injury. Further study of the biopsy, including as appropriate, immunohistochemistry and electron microscopy to favour secondary versus primary forms of injury, may help in further understanding of the spectrum of segmental lesions occurring in the transplant.

Combining all modalities of microscopic examination, along with key markers of podocyte injury and related phenomena, will probably in the future aid further understanding of this spectrum of diseases. In the meantime, renal biopsy remains the standard approach for understanding causes of nephrotic syndrome in patients. Expanding on current investigations of the renal biopsy to move firmly into the 21st century promises to add value to this traditional method of assessment. Now is the time to move forward with full characterization of the heterogeneous group of patients said to have FSGS so that we may increase our understanding and improve their outcomes.

Conflict of interest statement. None declared.

References
In this issue, Loureiro et al., studied the regulation of transforming growth factor beta-1 (TGF-β) signallng by bone morphogenetic protein-7 (BMP-7) in the biology of peritoneal dialysis-related peritoneal fibrosis. Peritoneal dialysis (PD) is a highly effective and convenient mode of renal replacement therapy, the success of which depends on the structural and functional integrity of the peritoneal membrane. Progressive alterations in peritoneal membrane transport characteristics commonly cause technique failure in PD, and are associated with fibroproliferative changes in the peritoneal membrane, including vasculopathy, accumulation of submesothelial extracellular matrix, and dedudation and altered appearance of mesothelial cells [1]. The fundamental causes of these changes are likely to be long-term exposure to bioincompatible dialysate, together with recurrent episodes of bacterial peritonitis.

Fibroproliferative diseases are largely driven by fibroblasts, spindle-shaped, motile, contractile cells that respond to pro-fibrotic stimuli by synthesizing and organizing extracellular matrix. Fibroblasts may originate from proliferation of local tissue fibroblasts, from circulating bone marrow-derived precursors (fibrocytes) and from resident epithelial cells by epithelial-to-mesenchymal transition (EMT) [2]. During EMT, epithelial cells lose intercellular adhesiveness and apical–basal polarity, and acquire a motile and contractile phenotype [3]. High-glucose concentrations typical of peritoneal dialysate induce such phenotypic change in mesothelial cells in vitro [4]. Additionally, the previous work of Yáñez-Mó et al. demonstrated progressive loss of epithelial morphology in mesothelial cells from peritoneal dialysis patients, and clear evidence for EMT of mesothelial cells over the course of peritoneal dialysis [5]. This was a key finding, because it strongly supported the notion that mesothelial cells, having undergone EMT, might orchestrate the adverse structural and functional alterations seen in PD patients.

Attention has subsequently focussed on mechanisms by which mesothelial cells undergo EMT in PD (reviewed in [6]). TGF-β, centrally important to fibrosis in many diseases, was strongly linked to EMT and fibrosis in PD in the work of Margetts et al., who demonstrated that, in rats, over-expression of TGF-β in the mesothelium recapitulates many of the peritoneal changes associated with membrane failure in chronic PD [7]. This is in keeping with the role of TGF-β more generally as a key driver of fibrosis and an inducer of numerous pro-fibrotic events, including EMT, fibroblast proliferation and matrix deposition [8]. However, TGF-β is ubiquitously expressed and, as well as being a powerful pro-fibrotic cytokine, plays key roles developmentally in cancer and in the regulation of inflammation and immunity [9,10]. Deletion of TGF-β has catastrophic consequences [11], and even relatively subtle