The glomerular tip lesion: What does it really mean?

Since its initial description by Howie and Brewer in 1984 [1], the glomerular tip lesion (GTL) has been a source of both confusion and controversy. As discussed below, much of the confusion relates to how the GTL is defined. The controversy seems more complex, however; once the confusion over terminology is resolved, it appears to boil down to two major issues: first, what is the relationship of the GTL to primary focal segmental glomerulosclerosis (FSGS), and second, what are the therapeutic implications of a diagnosis of GTL? While the resolution of the first of these issues will likely have to await more extensive molecular characterization of podocyte abnormalities in GTL, various histologic forms of FSGS, and minimal change disease (MCD), a reasonable approach to the second issue appears possible on the basis of our current knowledge, including the study of Howie et al [2] in this issue of Kidney International.

In their 1984 paper reporting 20 cases of GTL, Howie and Brewer [1] described a lesion involving a small area of the glomerular tuft that was always situated “adjacent to the origin of the proximal convoluted tubule, with adhesion to Bowman’s capsule.” They also noted that the rest of the glomerular tuft “appears normal by light microscopy but shows foot-process fusion by electron microscopy,” the latter consistent with the presentation of all of their patients with proteinuria of 3.5 to 30.6 g/day. Later, however, the definition of GTL became expanded to include lesions observed in the presence of other glomerular abnormalities and/or involving larger portions of the glomerular tuft. Howie [3] reported morphologic changes at the tubular origin resembling those in his original 20 cases of GTL in membranous nephropathy and other glomerulopathies characterized by persistent proteinuria. Howie [3] argued that these “tip changes” represent a secondary manifestation of protein leakage from the glomerulus, and that the prognosis in such cases is determined by the underlying glomerular pathology and not the tip changes. A corollary of this is that tip changes in the absence of other histologic abnormalities, such as in the original 20 cases of GTL, can be regarded as representing a variant of MCD, and indeed, tip changes were later demonstrated in autopsy specimens of kidneys from children with MCD who died from infections in the preantibiotic, precorticosteroid era [4].

Most recently, the term GTL has been used to define a specific histologic variant of FSGS. A pathologic classification of FSGS proposed by four leading renal pathologists (the “Columbia Classification;” [5]) defines the glomerular tip variant of FSGS by the presence of one or more segmental lesions involving the outer 25% of the glomerular tuft next to the origin of the proximal tubule, in the absence of perihilar sclerosis or collapsing FSGS. Stokes et al [6] recently compared 47 cases of GTL, defined as above, with 61 cases of MCD and 50 cases of FSGS not of the glomerular tip or collapsing types. Similar to findings of Howie and Brewer [1] and Beaman et al [7] in the original cases of GTL that were defined more stringently, Stokes et al [6] found that GTL patients closely resembled those with MCD with respect to high incidence (~90%) of nephrotic syndrome and paucity of chronic tubulointerstitial changes on the biopsy. Furthermore, as with earlier studies [1, 7, 8], more than 70% of GTL patients of Stokes et al [6] showed a reduction in proteinuria in response to treatment with steroids alone or plus a cytotoxic agent, with 59% having complete remission of proteinuria at a mean follow-up of 21.6 months.

In this issue of Kidney International, Howie et al [2] follow both the clinical and pathologic progression of segmental glomerular lesions associated with the nephrotic syndrome, including lesions limited to the tubular origin as in the original definition of GTL. The study presents three major findings relevant to the relationship of the GTL to FSGS and to MCD. First, histologic progression from GTL to FSGS with segmental lesions involving sites removed from the tubular origin [FSGS (NOS) per the Columbia Classification] is more than a rare occurrence. Seventeen of 24 patients with an initial renal biopsy showing GTL and one or more subsequent specimens (biopsy or autopsy) had findings of FSGS (NOS) on at least one subsequent specimen, while only 7 patients had GTL on all specimens. While these findings are clearly skewed by the fact that patients undergoing a second biopsy had persistent or relapsing proteinuria, they nonetheless suggest that progression of GTL to FSGS (NOS) is not uncommon. Second, GTL represents an early histologic finding

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**Key words:** glomerular tip lesion, focal segmental glomerulosclerosis, minimal change disease, nephrotic syndrome, renal biopsy.

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in patients who develop FSGS, although it remains unclear whether the GTL in these cases represents a manifestation of the FSGS itself or a nonspecific response to proteinuria occurring during the interval between initial podocyte injury and development of diagnostic segmental scars. Four patients who lost their native kidneys due to FSGS developed recurrent nephrotic syndrome in a total of 7 renal allografts; initial biopsies of 6 of these grafts showed GTL, with FSGS (NOS) seen on subsequent specimens from 2 of the grafts. Third, the clinical behavior of GTL that does not progress to FSGS resembles that of MCD, with response of proteinuria to steroids and/or other immunosuppressive agents and long-term renal survival [2].

Thus, it appears that GTL, whether defined by the original definition of Howie and Brewer [1] or the less restrictive one proposed in the Columbia Classification [5], represents a heterogeneous group of lesions that can behave like MCD or FSGS. Routine light and electron microscopy cannot distinguish good actors from bad, although in the future, immunohistologic studies of podocyte proteins whose expression is altered in FSGS but not MCD, or vice versa, may prove helpful in this regard. For now, only the response to treatment can reliably predict the outcome of the GTL, much as is the case with classic (NOS) and collapsing variants of FSGS [9]. Chun et al [9] found that among 11 nephrotic adults with a diagnosis of GTL, none of 7 who attained a complete or partial remission of proteinuria in response to steroid therapy developed end-stage renal disease (ESRD) after up to 10 years of follow-up, while 3 of 4 patients (including 1 of 2 who were not treated) not entering remission developed ESRD within 30 months. Thus, it would presently appear that the best advice for a nephrologist caring for a patient with a renal biopsy diagnosis of GTL, whether defined according to Howie and Brewer [1] or the Columbia Classification [5], would be to treat aggressively and hope for the best.

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