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Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion[1]

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Background. Several entities or variants within focal segmental glomerulosclerosis (FSGS) have been described, but their changes with time and interrelationships are undetermined.

Methods. Changes with time were studied in two series of segmental sclerosing lesions in the nephrotic syndrome, one of 22 specimens from ten patients in a trial, the other of 176 specimens from 121 consecutive patients.

Results. The earliest lesions were probably all at the tubular origin, equivalent to the tip variant of FSGS. In some patients, lesions remained at this site, but progression to renal failure was accompanied by morphologic progression, with development of lesions at various sites, equivalent to FSGS, not otherwise specified (NOS). Progression was more likely if there were large lesions, abnormal mesangium, and extensive acute tubular damage. Patients with lesions at the tubular origin at presentation had a shorter duration of symptoms and less chronic renal damage than those with multiple lesions, were more likely to have a complete response of the nephrotic syndrome, and were less likely to progress to renal failure. Recurrent nephrotic syndrome occurred in 12 of 14 allografts at risk, and was usually accompanied by lesions at the tubular origin, then multiple lesions.

Conclusion. At least some patients with FSGS (NOS) have evolved from the tip variant. The tip variant has been considered a distinct entity. Another interpretation is that it includes two conditions, one an early form of classic FSGS, and the other closely related to minimal change nephropathy (MCN), equivalent to the glomerular tip lesion as originally defined.

The term focal segmental glomerulosclerosis (FSGS) has been applied to segmental sclerosing lesions in different circumstances, such as in the nephrotic syndrome, nonnephrotic proteinuria, states of reduced renal mass, and various glomerular disorders. There is recognition that several morphologic entities have been included in FSGS [1]. Whether these are variants of a single condition has not been determined, nor has the relation between them. In particular, there has been little work on their changes with time.

The hypothesis of this study was that there were changes with time in segmental sclerosing lesions in the nephrotic syndrome. Our investigation was of two series of patients who had more than one specimen. The first series comprised patients with repeat specimens in the United Kingdom Medical Research Council (MRC) 1960 trial of steroids in the nephrotic syndrome [2]. Advantages of this series were that renal biopsies were collected without reference to the original diagnosis, patients who had a relapse usually had a repeat biopsy, and among later specimens were autopsy kidneys, which were virtually unobtainable afterwards. The second series comprised patients selected from all those with the nephrotic syndrome seen at one nephrology unit in 18 years, and had advantages that it was larger and more recent. Neither series included children under 13 years old.

METHODS

Repeat specimens in the MRC trial

In this trial, there were renal biopsies from 125 patients aged at least 15 years, with edema, at least 5 g proteinuria per 24 hours, and serum albumin concentration under 30 g/L [2]. Of 26 who had repeat specimens available for study [3], 16 were excluded with membranous nephropathy ($N = 8$), minimal change nephropathy (MCN) ($N = 5$), subendothelial membranoproliferative glomerulonephritis (MPGN) ($N = 2$), and severe late damage ($N = 1$). The ten patients studied had two renal biopsies ($N = 4$), a biopsy and an autopsy ($N = 4$), three biopsies ($N = 1$), and two biopsies and an autopsy ($N = 1$). One slide, usually with one section, was restained with periodic acid-methenamine silver (PA-silver), and examined for these features [4, 5]: number

[1] **See Editorial by Haas, p. 1188.**

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of glomeruli, number of glomeruli with identifiable tubular origin, number of globally sclerosed glomeruli, and whether mesangium appeared normal; appearance and size of segmental lesions, their position related to tubular origin and hilum, and number of glomeruli affected; and marked acute tubular damage, detected mainly as flattened epithelium, affecting at least a fourth of proximal tubules. Mesangium was considered normal if the amount of matrix and number of cells were not increased in comparison with those in reference glomeruli, for instance, in thin glomerular basement membrane disease. A large lesion occupied at least one third of the tuft. Epithelial changes in segmental lesions were defined as any changes in visceral epithelial cells, including crowding, swelling, vacuolation, and granulation. Any of the following features were called multiple lesions: (*1*) at least one lesion away from the tubular origin, such as at the hilum or mid tuft, and/or (*2*) lesions extending from tubular origin to hilum, and/or (*3*) lesions at various sites in glomeruli. Sections of autopsy kidneys were examined for a difference between outer and inner cortex, by drawing a line to split the cortex into two zones, counting glomeruli with segmental or global sclerosis, and expressing these as percentages of all glomeruli. A difference between the zones of at least 15% in either count was arbitrarily considered significant. Glomerular area was measured by an approximate method [6]. The index of chronic damage was calculated to measure damage as a proportion of cortical cross-sectional area [7]. Patterns of change in segmental abnormalities were identified.

Repeat specimens in the later series

Cases were selected from middle of 1985, following another study [8], to the end of 2003, from 730 consecutive patients aged at least 13 years with the nephrotic syndrome (edema, serum albumin concentration under 30 g/L, and proteinuria, at least 3.5 g/24 hours, or ratio of urinary albumin to creatinine concentrations of at least 300 mg/mmol). Patients were excluded with membranous nephropathy ($N = 218$), MCN ($N = 122$), diabetic glomerulopathy ($N = 65$), lupus nephritis ($N = 59$), amyloid ($N = 51$), acute postinfective glomerulonephritis ($N = 25$), MPGN ($N = 25$), IgA nephropathy/Henoch Schönlein nephritis ($N = 24$), light chain glomerulopathy ($N = 6$), vasculitic glomerulonephritis ($N = 4$), collapsing glomerulopathy ($N = 3$), eclamptic glomerulopathy ($N = 3$), immunotactoid glomerulopathy ($N = 3$), and cryoglobulinaemic glomerulonephritis ($N = 1$). This left 121 patients with at least one renal biopsy containing at least one segmental lesion. On electron microscopy, none had Alport syndrome or other identifiable inherited disorder. Of these 121 patients, 30 had more than one specimen, including specimens of renal allografts. Twenty-one had two biopsies, two had three, and seven had various biopsies ($N = 13$), nephrectomies ($N = 3$), allograft biopsies ($N = 15$), and allograft nephrectomies ($N = 6$). No autopsies were available. On every biopsy, there were at least six slides, with about six serial sections per slide. Sections were examined as in the MRC series. Nephrectomy kidneys were studied in the same way as MRC autopsy kidneys. Clinical features included treatment with immunosuppressive drugs (steroids, azathioprine, cyclosporine, cyclophosphamide, or mycophenolate mofetil), development of end-stage renal failure (ESRF), and nephrotic recurrence after transplantation. Response of proteinuria was incomplete, if persistently abnormal, or complete, if normal, either total below 0.2 g/24 hours or albumin/creatinine ratio below 3.0 mg/mmol. Renal status at follow-up was defined as well (normal function, and no proteinuria, as defined for complete response), or proteinuria, including the nephrotic syndrome (with normal function), or renal impairment (serum creatinine over 130 μmol/L, irrespective of proteinuria). Other outcomes were ESRF (onset of permanent dialysis), and death before dialysis, with either normal function or renal impairment. Outcomes were mutually exclusive.

Statistical methods

Wilcoxon's rank sum test was used to assess differences in the MRC series in glomerular area, index of chronic damage, and proportions of glomeruli with global sclerosis and segmental lesions. The *t* test was used to assess these factors in the later series, and also age, duration of symptoms, serum creatinine concentration, and length of follow-up. Survival rates to the earlier of ESRF or death, and to ESRF alone, were studied by the Kaplan-Meier method and log rank test, and by the life-table method. Spearman's coefficient was used to assess correlations between outcome and various factors. The Cox proportional hazards model was used to study the effect of different patterns of lesions on outcome, after controlling for these factors: index of chronic damage, proportion of glomeruli with global sclerosis, and proportion with global sclerosis and segmental lesions. The conventional value of $P < 0.05$ was considered significant.

RESULTS

Repeat specimens in the MRC trial

Patients fell into two groups, differentiated by findings in the last specimen (Table 1). MRC1 to MRC5 formed one group. These had segmental lesions in the first biopsy that were all at the tubular origin when their position could be determined, with foamy intracapillary cells or hyaline material or mixtures, and adhesion between basement membranes of capillary loops and Bowman's capsule (Fig. 1A to C). Epithelial changes were