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The Glomerular Mesangium in Hypertension

A Morphometrical Comparison of Nephrosclerosis with Mesangioproliferative Glomerulonephritis on Renal Biopsies

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Summary. Glomerular changes were morphometrically studied in renal biopsies of 27 cases of nephrosclerosis showing clinically benign or malignant hypertension and of 15 cases of mild mesangioproliferative glomerulonephritis with hypertension. In nephrosclerosis, there was a mild increase in mesangial matrix without cell proliferation. The degree of the mesangial changes varied little despite a large variation in blood pressure and showed no significant difference between benign and malignant hypertension. In mild mesangioproliferative nephritis with hypertension, mesangial matrix, as well as the number of mesangial cells, showed an increase of varying degree. A quantitative assessment of the mesangium was proved effective in differentiating the glomerular changes in nephrosclerosis from those in mesangioproliferative nephritis with hypertension.

Key words: Hypertension — Mesangioproliferative nephritis — Mesangial matrix — Mesangial cell — Morphometry.

A considerable number of observations have reported glomerular changes in benign and malignant nephrosclerosis, such as degeneration, necrosis, cell proliferation, exudation, hyalinization, atrophy and collapse of the tuft capillary (Löhlein, 1916; Volhard, 1918; Fahr, 1925; McGregor, 1930; Klemperer and Otani, 1931). These glomerular changes are essentially focal or local in distribution and usually involve only a small number of glomeruli. As a diffuse change of the glomerulus in nephrosclerosis, on the other hand, there is a mild increase of mesangial matrix, to which little attention has been paid in the literature (Kimmelstiel, 1935). Owing to this diffuse change of the mesangium, however, it is often difficult to find a histological difference between nephrosclerosis and mild mesangioproliferative glomerulonephritis accompanied by hypertension, both of which are clinically as well difficult to be differentiated from each other. In order to study this practical problem in the differential diagnosis, mesangial volumes and the number of glomerular cells in the two groups were morphometrically estimated and compared on biopsy material.

Material and Methods

As study groups, 27 cases of benign or malignant nephrosclerosis and 15 cases of mild mesangioproliferative glomerulonephritis with hypertension were selected from the biopsy files of the Institute of Pathology, University of Tübingen. Nephrosclerotic cases showing

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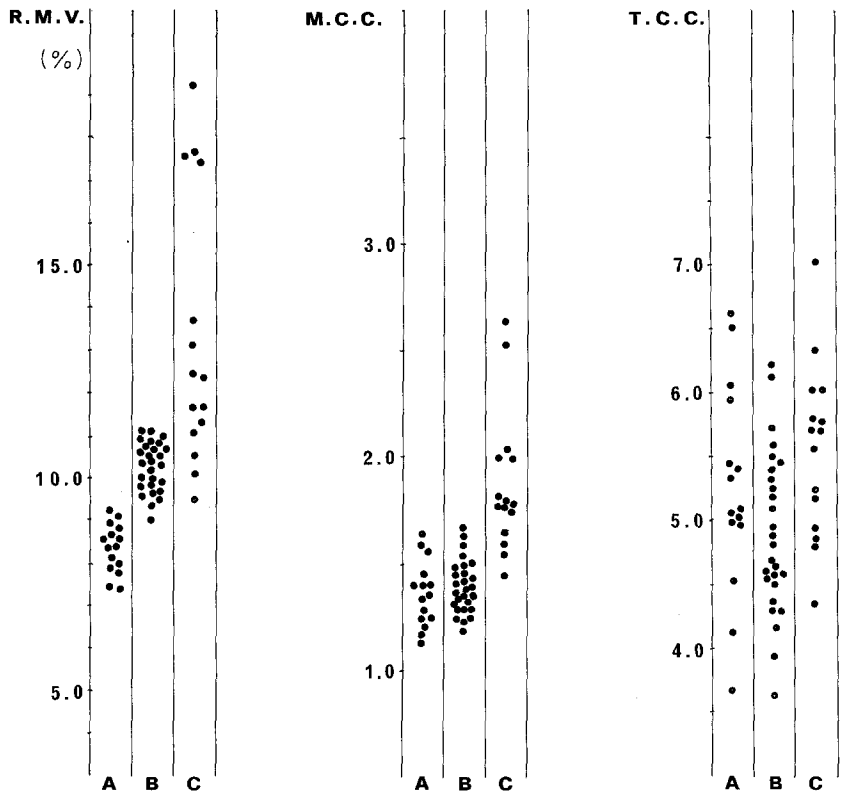

Fig. 1 A–C. Distributions of values for relative mesangial volumes (R.M.V.), mesangial cell counts (M.C.C.) and total glomerular cell counts (T.C.C.). (A) Controls. (B) Nephrosclerosis with hypertension. (C) Mesangioproliferative nephritis with hypertension

proteinuria ($\geqq 0.5$ g/day) and glomerulonephritics with slight proteinuria ($\leqq 0.6$ g/day) had been excluded in order to eliminate questionable cases. Hypertension was defined as blood pressures above 150 mmHg systolic or above 90 mmHg diastolic.

The controls consisted of 15 biopsy cases ranging in age from 19 to 48 years, which had been diagnosed as unremarkable. All cases of the controls had normal blood pressures.

Glomerular mesangial volumes were measured by the pointcounting method (Wehner, 1968; Hara, 1972) and the degree of mesangial thickening was presented by a ratio of mesangial volume to the total volume of the glomerular tuft, i.e., by the relative mesangial volume. The point-counting was made on 4 to 5μ sections stained with periodic-acid-Schiff at a magnification of $\times 500$ by using an eyepiece incorporating a square lattice with 361 points.

Mesangial cells and total glomerular cells (i.e., mesangial, endothelial and epithelial cells) were counted and represented by the number of cells per 1000 μ^2 glomerular area, respectively.

On the morphometrical procedure described above, the glomeruli showing focal or local changes, such as degeneration, necrosis, cell proliferation, hyalinization, atrophy and collapse of the tuft capillary, were excluded and only the glomeruli of a same appearance were measured.

Results

1. Nephrosclerosis with Hypertension

Of the 27 cases studied, 18 were histologically benign nephrosclerosis and 4 were malignant nephrosclerosis, the other 5 being borderline or transitional. The

Table 1. Values for the relative mesangial volume and the cell count

	Controls	Hypertension	Mesangioproliferative glomerulonephritis
Number of cases	15	27	15
Relative mesangial volume (Mean ± S.D.)	8.36 ± 0.57%	10.25 ± 0.57%	13.30 ± 3.12%
Mesangial cell count per 1000 μ^2 gl. area (Mean ± S.D.)	1.37 ± 0.15%	1.40 ± 0.12%	1.88 ± 0.34%
Total cell count per 1000 μ^2 gl. area (Mean ± S.D.)	5.25 ± 0.80%	4.91 ± 0.63%	5.57 ± 0.69%

Table 2. Comparison of the relative mesangial volume and the cell count in benign hypertension with those in malignant hypertension

	Benign hypertension	Malignant hypertension
Number of cases	13	14
Range of blood press.	160/90 ~ 180/130 mm Hg	180/135 ~ 280/180 mm Hg
Mean of systolic blood press.	180.8 mm Hg	231.4 mm Hg
Mean of diastolic blood press.	110.8 mm Hg	156.5 mm Hg
Relative mesangial volume (Mean ± S.D.)	10.23 ± 0.56%	10.27 ± 0.61%
Mesangial cell count per 1000 μ^2 gl. area (Mean ± S.D.)	1.40 ± 0.12	1.41 ± 0.13%
Total cell count per 1000 μ^2 gl. area (Mean ± S.D.)	4.76 ± 0.62	5.05 ± 0.63

mean age at biopsy was 37.3 years with a range of 17 to 52 years. The blood pressure ranged from 160 to 280 mmHg systolic and from 90 to 180 mmHg diastolic.

The mesangial volume was mildly increased as compared with the controls ($p < 0.001$, Fig. 1, Table 1). This mild increase in mesangial matrix was diffuse in distribution and involved almost all the glomeruli.

The number of mesangial cells and that of total glomerular cells stayed within the normal range (Fig. 1, Table 1).

As noted in Table 2, the nephrosclerotic cases were divided into two groups according to the definition that diastolic blood pressures of 130 mmHg or less belong to benign hypertension and diastolic pressures over 130 mmHg to malignant hypertension. Neither the mesangial volume nor the mesangial and total cell count showed any significant difference between benign and malignat hypertension (Table 2).

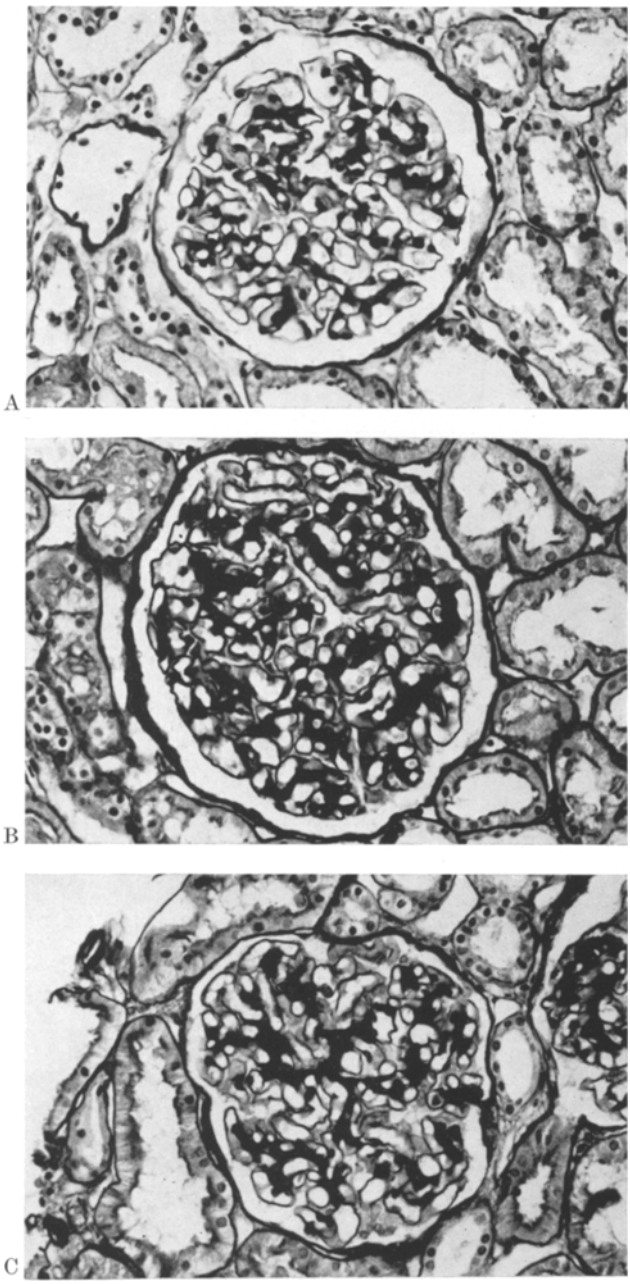

Fig. 2 A–C. Histological comparison of glomeruli. (A) Control (73/10/154. A 25-year-old man with normal blood pressure. PAS. ×225). (B) Nephrosclerosis with hypertension (74/11/46. A 27-year-old woman with blood pressure, 200/120 mmHg. PAS. ×225). (C) Mesangioproliferative nephritis with hypertension (74/10/70. A 46-year-old woman with blood pressure, 170/100 mmHg. PAS. ×225)

2. Mesangioproliferative Nephritis with Hypertension

The mean age of the 15 patients was 37.9 years with a range of 17 to 59 years. The blood pressure ranged from 150 to 210 mmHg systolic and from 90 to 140 mmHg diastolic. No case underwent dialysis in the present study.

The mesangial volume and the number of mesangial cells showed an increase of varying degree, respectively ($p < 0.001$, Fig. 1, Table 1). The number of total glomerular cells was not significantly increased ($p > 0.05$) in spite of the increase in the number of mesangial cells. This is attributed to a large variation in the total glomerular cell count in both of the controls and the study cases.

3. Comparison between Nephrosclerosis with Hypertension and Mesangioproliferative Nephritis with Hypertension

The histological feature of the glomerular changes in nephrosclerosis was similar to that in mild mesangioproliferative nephritis (Fig. 2). As presented in Fig. 1, however, the variation in the degree of the mesangial thickening was very small in the former, while it was large in the latter. In addition, there was no proliferation of mesangial cells in nephrosclerosis, while the number of mesangial cell was increased in the majority of glomerulonephritic cases ($p < 0.001$). The number of total glomerular cells in mesangioproliferative nephritis was larger than that in nephrosclerosis ($0.001 < p < 0.01$).

In 5 of the 15 glomerulonephritic cases, the value for the mesangial volume was not different from that in nephrosclerosis ($p > 0.02$, Fig. 1). Each of these 5 cases, however, showed an increase in the number of mesangial cells ($p \leqq 0.003$), which did not occur in nephrosclerosis. Another 4 of the glomerulonephritics had no significant increase in the number of mesangial cells ($p > 0.02$, Fig. 1), but the mesangial volume of each of the 4 was significantly larger than that in nephrosclerosis ($p \leqq 0.006$).

Discussion

Mesangial changes in hypertension are characterized by a diffuse increase in matrix without cell proliferation. The degree of the changes varied little despite a large variation in blood pressure and showed no significant difference between benign and malignant hypertension in the present study. Proliferation of cells of the glomerular tuft and of those lining Bowman's capsule are sometimes prominent in malignant nephrosclerosis, as pointed out by several authors (Volhard, 1918; Fahr, 1925; Klemperer and Otani, 1931). However, these proliferative changes in malignant nephrosclerosis usually occur in association with necrosis or severe degeneration of the glomerular tuft and are focal or local in distribution. There was no increase in the number of mesangial cells even in malignant nephrosclerosis, under the condition that the glomeruli showing focal or local changes were excluded and only the glomeruli of a same appearance were measured.

An aging process also brings about a mild increase in mesangial matrix, which apparently develops independently of hypertension (Kimmelstiel, 1935; Wehner, 1968; Hara, 1972). However, the mesangial changes in aging tend to be milder than those in hypertension. An effect of ischemia may relate to the mesangial changes in both hypertension and aging, though the mechanism involved in the

mesangial hyalinosis remains obscure. In chronic glomerulonephritis with hypertension, the mesangial hyalinosis in hypertension may be superimposed on glomerular lesions resulting from an inflammatory process (Meyer, 1974).

In 6 of the 15 cases of mild mesangioproliferative nephritis, both of the mesangial volume and the mesangial cell count were larger than those in benign or malignant hypertension. In the other 9 cases, either the mesangial volume or the mesangial cell count was larger than the values in hypertension. Accordingly, in the present study, glomerular changes in hypertension could be differentiated from those in mild mesangioproliferative nephritis by estimating mesangial volumes and mesangial cell counts. This result indicates that the quantitative analysis of the mesangium is effective in differentiating between the glomerular changes in hypertension and those in mild mesangioproliferative nephritis, both of which are sometimes histologically very similar to each other.

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