Early Lesions of the Nephron in Paraproteinemia

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Paraproteinemia may be considered as a prerenal alteration of protein metabolism causing secondary lesions in the kidney. Of importance in this disorder is an increased amount of immunoglobulin fragments which partially permeate the glomerulus and may be demonstrated in the final urine as Bence-Jones proteins. Our paper discusses whether in paraproteinemia there are already lesions in the nephron of patients without impairment of renal function.

Materials and Methods

Kidney biopsies were performed on eight patients with an average age of 58 years: six had multiple myeloma (three IgG, one IgA, two Bence-Jones plasmocytoma), one had Waldenström's disease, and one had idiopathic paraproteinemia. Diagnosis was confirmed by immune electrophoresis and sternal puncture; in the patients with plasmocytoma by demonstration of a Bence-Jones proteinuria. The patient with the idiopathic paraproteinemia was considered as a control since he had not been treated with a combination of steroids and cytostatics like the other patients. In all patients, creatinine clearance was normal according to age. Quantitative proteinuria was not increased substantially (0.2 g/24 h), even in Bence Jones proteinuria.

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Fig. 1. Glomerulus. a Survey with three capillary loops. Mesangium with increased matrix, deep invagination of the nucleus. Continuity of increased fibrillar mesangial matrix and irregular thickening of the lamina rara interna. Podocytes appearing normal with several mitochondria in the cytoplasm. b Basement membrane with thickening of the endothelial side by fine and coarse fibrillar material, notching of the endothelial layer. Pedicles of the podocytes intact with slit membranes and glycocalyx. Magnification: a = 6,200 x; b = 46,000 X.

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For electron microscopy, samples of the renal biopsies from cortex and outer medulla were fixed in a mixture of aldehydes, post-fixed in osmium tetroxide and embedded in plastics (Epon 812). Semi-thin sections were stained with alkalized toluidine blue and the thin section with uranyl acetate followed by lead citrate. Electron microscope: Siemens Ia.

Results

In light microscopy the only remarkable alteration is a slight enlargement of the mesangium. The proximal tubules display discrete signs of apical vacuolization.

In contrast, electron microscopy of the nephron shows in all patients impressive lesions confined to glomeruli and proximal tubules. In the glomerulus the mesangium is enlarged by deposits of fine fibrillar material without periodicity between the extensively developed cell processes. In a continuous way similar material is seen in the lamina rara interna causing an irregular thickening of the basement membrane (fig. 1a). At a higher magnification this material consists of fine and coarse fibrils lacking any periodicity. The lamina densa and rara externa are apparently intact and the endothelial cell layer is deeply notched and deformed (fig. 1b). The proximal tubules show large resorption vacuoles in the apical zone and many dense bodies (fig. 2). Below the brush border there are numerous endocytic vesicles and tubules with an inner and outer fuzzy coat. Besides these, many electron dense apical tubules are noticeable. Some of these are enlarged and encompass parts of the cytoplasm or completely cover electron translucent areas (fig. 3 a). The smooth endoplasmatic reticulum is extensively developed. Conspicuous are deposits of fibrillar and circularly arranged structures in the basement membrane (also to be found in very small numbers in the capillary basement membrane and the mesangium of the glomerulus) the largest ones exhibiting a width of 45 nm and a periodicity of 10 nm (fig.3 b). In only one patient could typical amyloid deposits be seen (fig. 3 c).

Discussion

In the glomerulus we would like to interpret the fibrillar material without periodicity causing the enlargement of the mesangium and the thickening of the
lamina rara interna of the capillary basement membrane as precursor of amyloid fibrils. Two experimental findings are in support of this hypothesis: first, according to Beneke (1971), amyloid is generally thought to be a cellular product synthesized in the glomerulus by the mesangial cells and primarily deposited in the mesangial matrix and lamina rara interna of the capillary basement membrane. Second, Glenner et al. (1973) and Terry et al. (1973) demonstrated a very close structural relation between Bence-Jones protein and amyloid fibrils. Until recently of the very few electron microscopic studies of kidneys in multiple myeloma, only specimens which displayed exceptionally severe lesions already detectable by light microscopy and mostly considered in accordance with so-called myeloma kidney had been examined. In patients with renal insufficiency frequently combined with nephrotic syndrome, Abrhms et al. (1966), found fibrillar and granular material in the basement membrane, whereas Kahn et al. (1969) described amyloid deposits, and Fisher et al. (1964) the focal thickening of the mesangium and basement membrane. These variations in findings are probably dependent on the examination of patients with very different clinical stages and courses of this disease.

The alterations in the proximal tubules with discrete vacuolization and large amounts of dense bodies are in agreement with the experimental findings in protein reabsorption (Munsbch, 1966; Munsbch nd Neustein, 1968; Thoenes et l., 1970). Extensive development of smooth endoplasmatic reticulum may be related to intoxication as shown in experiments by McDowell (1974).

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The unique fibrillar structures with a definite periodicity in figure 3b can be compared with the fibrils of Brity et l. (1973) and Schuurms Steckhoven nd Vn Helst (1973) which were found in lupus erythematosus and glomerulonephritis, and are probably immunoglobulins. In our case, we suggest that these structures may consist of large aggregates of immunoglobulin fragments. Summarized, our findings in the nephron of patients with paraproteinemia are thought to be a contribution to the pathomorphogenesis of the myeloma kidney.

Summary

Electron microscopy of renal biopsies in eight patients with paraproteinemia (six multiple myeloma, one Waldenström's disease, one idiopathic paraproteinemia) and without impairment of renal function demonstrates an increase of mesangial matrix and thickening of the lamina rara interna of the basement membrane in the glomerulus by fibrillar material
without periodicity. These lesions are thought to exhibit precursors of amyloid deposits. The proximal tubules show signs of increased cellular activity probably because of handling an increased protein load. In the basement membranes there are proteins with a fibrillar structure and definite periodicity. These are suggested to be consistent with large aggregates of immunoglobulin fragments.

References


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