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Simultaneous Occurrence of Perimembranous Glomerulonephritis and Glomerular Amyloidosis

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Summary. The results of electron microscopic examination of renal biopsies from 3 patients with rheumatoid arthritis treated with penicillamine are presented. All 3 patients developed a nephrotic syndrome upon discontinuation of penicillamine therapy. When viewed with the electron microscope, segmental forms of perimembranous glomerulonephritis (Stages I–II of Ehrenreich and Churg) and glomerular renal amyloidosis Grade I–III were observed. In all three cases the nephrotic syndrome was considered to be due to the simultaneous occurrence of the two disease processes. In 2 cases perimembranous glomerulonephritis with immuno-complex-deposits was assumed to be the dominant factor in the causation of the disease, in the other case amyloidosis was the principle abnormality.

Key words: Perimembranous glomerulonephritis – Glomerular amyloidosis – Therapy with D-penicillamine.

The investigations of Watanabe and Saniter (1975) on our biopsy material have shown that in Western Germany rheumatoid arthritis (R.A.) plays a leading role in the development of scondary renal amyloidosis.

Furthermore, Gärtner et al. (1975) have observed that patients with rheumatoid arthritis treated with penicillamine often develop a peri-, extra-, or epimembranous glomerulonephritis. From these studies it might be expected that occasional patients with R.A. would develop glomerular amyloidosis and perimembranous glomerulonephritis simultaneously.

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In the last 2 years we have observed 5 cases of glomerular amyloidosis and perimembranous glomerulonephritis in patients with R.A. treated with penicillamine. Three of these cases will be briefly reported:

Case 1. D. M., a 57-year-old female. History: rheumatoid arthritis, treated for 1 year with 1200 mg/day D-penicillamine (total dose 432 g); appearance of proteinuria was first noted 3 months after discontinuation of penicillamine therapy.

On admission the nephrotic syndrome was present (total protein 4.8 g/100 ml, proteinuria 5.9–9%), serum creatinine 0.6 mg/100 ml, Hb 10.6 g/100 ml, blood pressure 120/70 mm Hg. Renal biopsy in September 1975 (75/9/732), showed segmental perimembranous glomerulonephritis Stage I (Ehrenreich and Churg). Minor perireticular renal amyloidosis (degree 1) was present with amyloid fibrils in the expanded mesangium and in the adjacent basement membrane. Scattered amyloid was also found in zones away from the mesangium, within the basement membrane and at its periphery, with predominantly radial deposition of fibrils. There was some apparent loosening of the glomerular epithelial cells by amyloid fibrils infiltrating the basement membrane. In other areas, free of amyloid, immunodeposits in the subepithelial layer of the basement membrane were seen, some of these having spike-shaped protuberances (Fig. 1a and b). The amyloid-laden areas of the basement membrane were either free of immunoprecipitates or showed only indistinct deposits.

Case 2. H.H., a 52-year-old male with a history of rheumatoid arthritis since 1970. Therapy with Indomethacin, Azathioprine and ACTH, with slight improvement. March 1972 proteinuria (+) was noted. In summer 1973 a change in therapy to 1200 mg/day D-penicillamine therapy followed until March 1975. In July 1975 there was swelling of the ankles and fatigue. On admission a total serum protein of 4.8 g/100 ml, urine protein excretion 2.5–10‰, Hb 11.5 g/100 ml, serum creatinine 1.6 mg/100 ml, blood pressure 120/80 mm Hg were found. There was persistent proteinuria with Esbach values around 5‰ and lowered total serum protein values (5 g/100 ml) until December 1975. Renal biopsy was performed in October 1975 (75/10/207) and showed Grade II–III perireticular renal amyloidosis with distinct nodular amyloid deposits in the mesangium, subendothelially, and with occasionally spindle-shaped distensions of the basement membrane in areas away from the measangium. In addition there was segmental development of a Stage I perimembranous glomerulonephritis (Ehrenreich and Churg) in the area of the basement membrane containing no amyloid fibrils. Finally there were areas where the basement membrane showed neither immunoprecipitates nor amyloid fibrils and where the foot processes of the glomerular epithelial cells appeared normal.

Case 3. G. St., a 59-year-old male with a history of rheumatoid arthritis since 1963. Gold therapy in 1965 was discontinued after 5 injections due to hypersensitivity and steroid therapy was given for several years. D-penicillamine treatment was begun in May 1975 at 300 mg/day, increasing up to 900 mg/day. Improvement of the underlying disease occurred together with manifestation of proteinu-

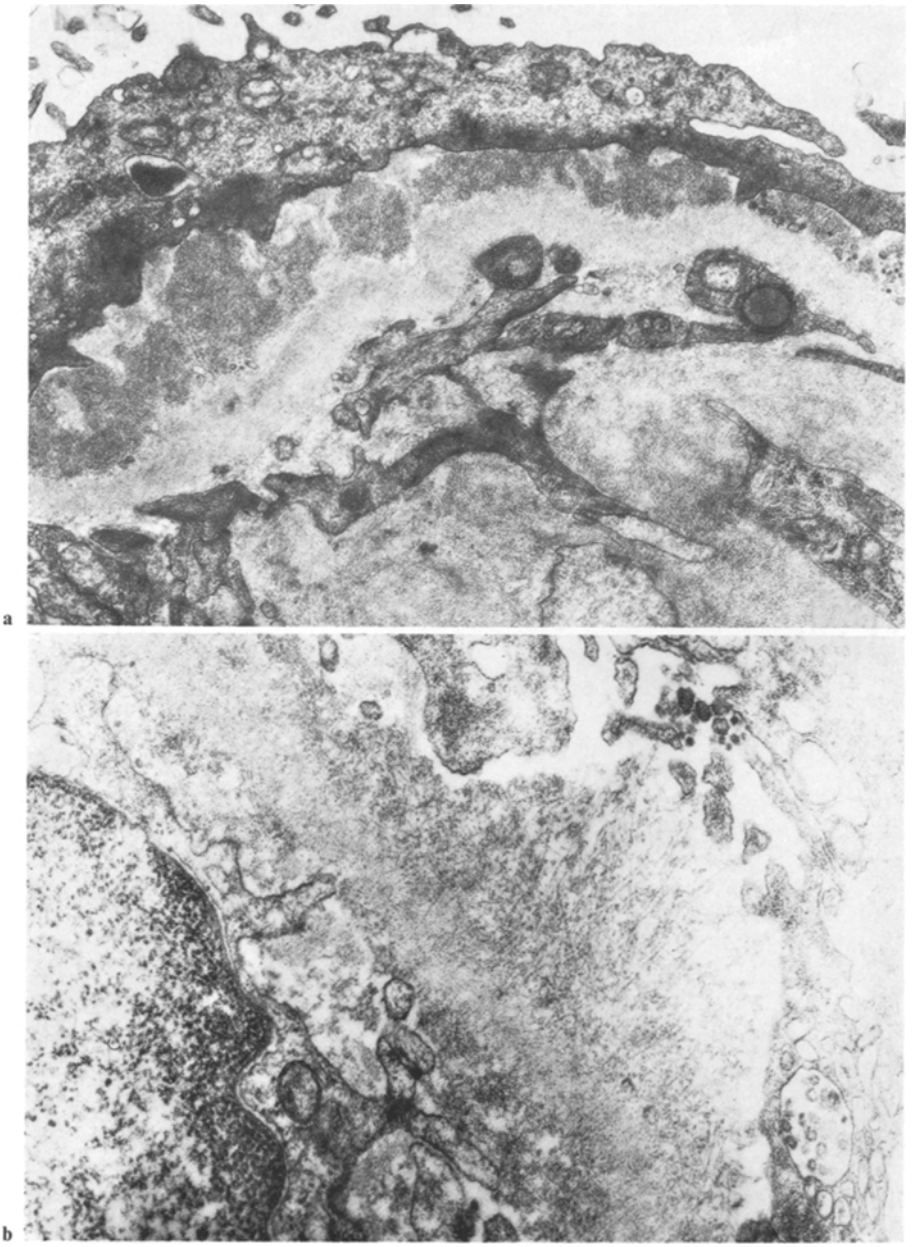

Fig. 1. a Subepithelially located deposits with spike-shaped protuberances between the immunodeposits. The foot-processes are fused. 25,000:1. **b** Amyloid fibrils in the basement membrane, prolapsing in a radial direction into the Bowman's capsule. Loosening of the foot processes of the basement membrane in this area. Lack of immunodeposits in this part. (Partial view of a glomerulus.) 42,000:1

ria. In October 1975 the penicillamine treatment was discontinued. On admission in October 1975 laboratory findings included total serum protein 5 g/100 ml, urinary protein excretion 9‰, serum creatinine 1.4 mg/100 ml, blood pressure 130/65 mm Hg, Hb 17.5 g/100 ml, absence of polycythemia. Renal biopsy was performed in November 1975 (75/11/859) and showed grade II perireticular renal amyloidosis with amyloid deposits in the mesangium and in and on both sides of the basement membrane. At the periphery isolated sections of the lamina-densa could be observed next to amyloid bundles which penetrated radially towards the basement membrane. In those basement membrane zones free of amyloid deposits densely located immunoprecipitates were found, separated from one another by small spike-shaped protuberances of the basement membrane (perimembranous glomerulonephritis Stage II, Ehrenreich and Churg, 1968). Furthermore, one can see that the deposits of immunoprecipitates do not appear in all amyloid-free zones of the basement membrane. The foot processes of the glomerular epithelial cells are fused where the basement membrane is either infiltrated or surrounded by amyloid fibrils, or in the outer layer of the basement membrane where immunoprecipitates are present. In the remaining areas, normal foot processes are present, although a nephrotic syndrome was present at the time of biopsy.

Discussion

As reported here, all 3 cases of Grade I–III perireticular renal amyloidosis were accompanied by a perimembranous glomerulonephritis of Stage I–II (Ehrenreich and Churg) of a segmental character. Especially noteworthy is that the immunodeposits typical for perimembranous glomerulonephritis were only barely detectable in areas where amyloid fibrils infiltrated the basement membrane of the glomerular capillaries and were deposited in the subepithelial and subendothelial layers of the basement membrane. Similarly, no immunoprecipitates could be found in the area of so-called basement membrane denudation which all 3 cases showed to varying extent. Except for those areas of the basement membrane showing denudation of epithelial covering, the foot processes of glomerular epithelial cells were swollen or fused where subepithelial amyloid fibrils or subepithelial immunoprecipitates were deposited. In the remaining areas normal foot processes were found, although a nephrotic syndrome was present at the time of renal biopsy.

Many cases of glomerular renal amyloidosis and perimembranous glomerulonephritis are accompanied by the nephrotic syndrome. Analyzing our data, Watanabe and Saniter (1975) found a nephrotic syndrome in more than 50% of the cases with Grade I amyloidosis and in more than 80% in Grades II and III. Perimembranous glomerulonephritis in stage I and II is associated with the nephrotic syndrome in 70 and 77% of cases, respectively (Gärtner et al., 1977). From these results it may be concluded that the proteinuria in cases of simultaneous occurrence of perimembranous glomerulonephritis and glomerular amyloidosis is due to both kinds of glomerular injury. The alteration of epithelial slits by subepithelially deposited immunoprecipitates in perimembra-

nous glomerulonephritis and of the basement membrane areas where denudation of the epithelial covering occurs in amyloidosis presumably leads in the same way to proteinuria.

In amyloidosis there is a significant negative correlation between the level of total serum proteins and the extent of the amyloid interspersed basement membrane areas with denudation of the epithelial covering (Gise et al., 1978). In case 1 as well as in case 3, such basement membrane areas with denudation of the urinary aspect were seldom observed. We therefore conclude that in these two cases the nephrotic syndrome was caused mainly by basement membrane transformation in perimembranous glomerulonephritis. In case 2, however, many areas showing basement membrane denudation could be counted.

For this reason we believe that in case 2 the nephrotic syndrome was due mainly to the presence of amyloid interspersed basement membrane areas with denudation of the pithelial covering; the accompanying perimembranous glomerulonephritis being an additional factor.

A possible connection between penicillamine therapy and the nephrotic syndrome is supported by the fact that the proteinuria and the nephrotic syndrome in the 3 patients with R.A. invariably developed either during the application or within a short time after the discontinuation of penicillamine therapy. These findings confirm earlier studies on 31 patients (Gärtner et al., 1975) treated with penicillamine who all developed proteinuria or the nephrotic syndrome. The morphologic changes in all these cases were those of a perimembranous glomerulonephritis of a partially segmental character. Although penicillamine has not yet been identified as an antigen, it is likely that it leads to the formation of immune complexes through a hapten-effect which then deposit themselves in the subepithelial layer of the glomerular basement membrane, as in perimembranous glomerulonephritis. This results in an increase in the permeability of the basement membrane and to the epithelial slits, leading to proteinuria and the deveopment of the nephrotic syndrome. The amyloidosis present in all 3 cases contributes an additional factor to the pathogenesis of the nephrotic syndrome.

Despite its undoubted value in the treatment of severe cases of R.A., it is uncertain whether penicillamine is of value in the treatment of amyloidosis (Lake and Andrews, 1968; Wright et al., 1972; Bryde and Missmahl, 1975); furthermore it is possible that it may lead to a deterioration of amyloidosis.

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