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Ultrastructure of spontaneous glomerular lesions in Syrian hamsters of APA strain

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Summary. Electron microscopic observations were carried out on the spontaneous glomerular lesions in male APA hamsters from 3 to 12 months of age. Until 6 months of age, focal expansion of mesangial region due to an increase of matrix material and mesangial cells was characteristic, and segmental thickening of capillary basement membrane and partial effacement of foot processes of podocytes were also sometimes observed. At 12 months of age, although all of these changes became more severe, the most prominent alteration was found in podocytes, which showed various degenerative changes. No deposition of amyloid fibrils was detected in any portion of the glomerulus.

Key words: Aging, APA hamster, Glomerular lesion, Ultrastructure

Introduction

Syrian hamsters of the APA strain (APA hamsters) have been developed in Japan (Tajima, 1968) and maintained as a closed colony by random breeding in our laboratory since 1988. APA hamsters are known to develop spontaneous mesangial thickening in the renal glomeruli from a young age (Han et al., 1992a). At and after 6 months of age, they also develop focal and segmental glomerulosclerosis (FSG), of which the severity increases quickly after 12 months of age, resulting in death in some populations (Doi et al., 1987). Histochemical examinations of aged APA hamsters (Doi et al., 1987) did not reveal glomerular amyloidosis which is the most common renal lesion in aged Syrian hamsters of other strains (Gleiser et al., 1971; McMartin, 1979; Mezza et al., 1984). Recently, Han et al. (1992b) succeeded in a rapid induction of glomerular lipidosis and FSG in APA hamsters by streptozotocin.

This paper describes the ultrastructural progression of spontaneous glomerular lesions in male APA hamsters from 3 to 12 months.

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Materials and methods

Fifteen male APA hamsters were used. They were maintained under controlled conditions (temperature, 24 ± 1 °C; humidity, 55 ± 5%) in plastic cages with sterilized wood shavings for bedding, and fed a commercial diet, CMF (Oriental Yeast Co. Ltd., Tokyo) with tap water *ad libitum*. Five animals were weighed and killed by exanguination under ether anaesthesia at 3, 6 and 12 months of age, respectively. The kidneys were weighed and fixed in 10% neutral-buffered formalin, and 2 μm - paraffin sections were stained with haematoxylin and eosin (HE) or periodic acid-Schiff (PAS). For electron microscopic examination, small pieces of the renal cortex were fixed in 2.5% glutaraldehyde and 2.0% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4), postfixed in 1.0% osmium tetroxide in the same buffer, and embedded in epoxy resin, Quetol 812 (Nisshin EM Co. Ltd., Tokyo). Ultrathin sections were double-stained with uranyl acetate and lead citrate.

Results

Body and kidney weights

Body and kidney weights increased correlatively with aging, and the kidney to body weight ratio was constant throughout the experimental period (Fig. 1).

Light microscopic findings

At 3 months of age, mild mesangial thickening was

detected in some glomeruli (Fig. 2a). Mild glomerulosclerotic lesions developed sporadically in juxtamedullary cortex at 6 months of age (Fig. 2b). FSG progressed and extended from juxtamedullary cortex to subcapsular cortex at 12 months of age. In addition, Bowman's capsules enclosing severely affected glomeruli showed prominent thickening of their basement membranes (Fig. 2c). On the other hand, only focal degenerative and/or regenerative changes were sporadically observed in the uriniferous tubules up to 12 months of age.

Electron microscopic findings

Up to 6 months of age, the most characteristic ultrastructural change of the glomeruli was a focal expansion of the mesangial region due to an increase of matrix material and mesangial cells (Fig. 3). Mild segmental thickening of capillary basement membrane and partial effacement of foot processes of podocytes were also observed in some glomeruli (Fig. 4).

At 12 months of age, the above-mentioned changes in mesangial region and capillary basement membrane became more prominent in a large number of glomeruli (Fig. 5). In some expanded mesangial regions, lipid deposition and mesangial cell degeneration were also observed (Fig. 6). Not infrequently, a part of the mesangial cell cytoplasm migrated into the capillary basement membrane, resulting in a thickening of the capillary basement membrane (Fig. 7), or it protruded into the capillary lumen (Fig. 8). Amyloid fibrils were never detected in any portion of the glomeruli.

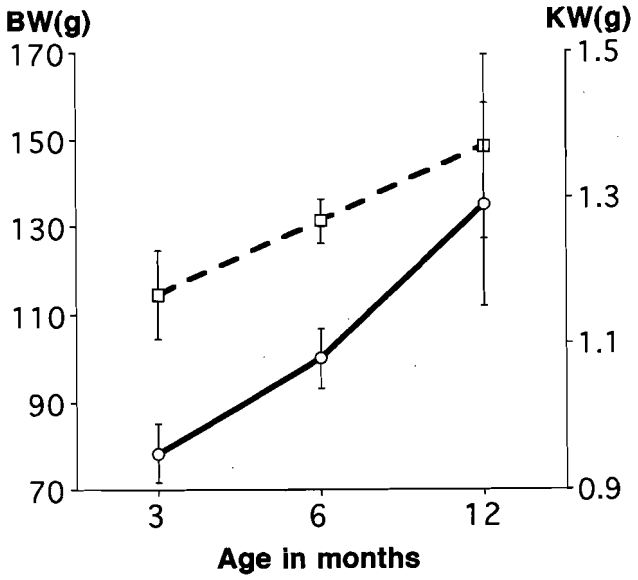

Fig. 1. Changes in body and kidney weights of APA hamsters. squares: Body Weight (BW); circles: Weight of Kidneys (KW).

The most prominent ultrastructural glomerular change at 12 months of age was found in podocytes. Namely, broad sheets of their cytoplasm were often directly applied to the outer surface of the capillary basement membrane (Fig. 7). In addition, podocytes frequently exhibited various degenerative changes, such as mild dilatation of rough endoplasmic reticula (Fig. 5), formation of myelin figures

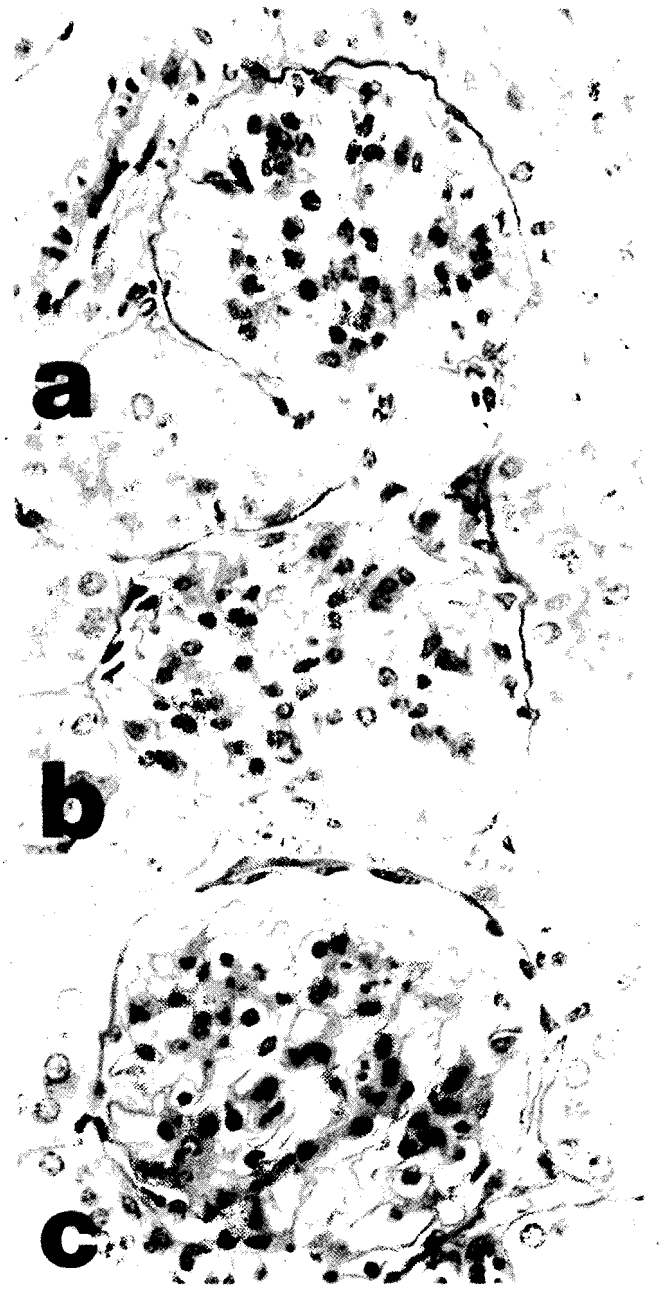

Fig. 2. Light microscopic picture of glomeruli of APA hamsters at 3 **(a)**, 6 **(b)** and 12 months of age **(c)**. Focal expansion of mesangial region becomes more severe with aging. Apparent FSG is seen in (c). PAS. x 480

(Fig. 8), vacuolization of cytoplasm (Fig. 9) and disappearance of a normal cytoplasmic structure (Fig. 10).

In the wall of Bowman's capsule, cytoplasmic processes of epithelial cells generally encroached into the thickened basement membranes. An accumulation of glycogen granules was rarely observed in the cytoplasm of epithelial cells (Fig. 11).

Discussion

Light microscopic findings of renal glomeruli of APA hamsters coincided with those previously reported (Doi et al., 1987), and the lesion occurred first in the juxtamedullary glomeruli and then extended to the subcapsular glomeruli as reported in the development of human FSG (Mizoguchi and Iidaka, 1987).

In this study, ultrastructural development of spontaneous renal glomerular lesions in APA hamsters from 3 to 12 months of age has been clarified for the first time. In the early glomerular lesions, the most prominent changes were found in mesangium and the less prominent ones in capillary basement membranes and podocytes.

At 12 months of age, changes in all of these glomerular components became more severe. Namely,

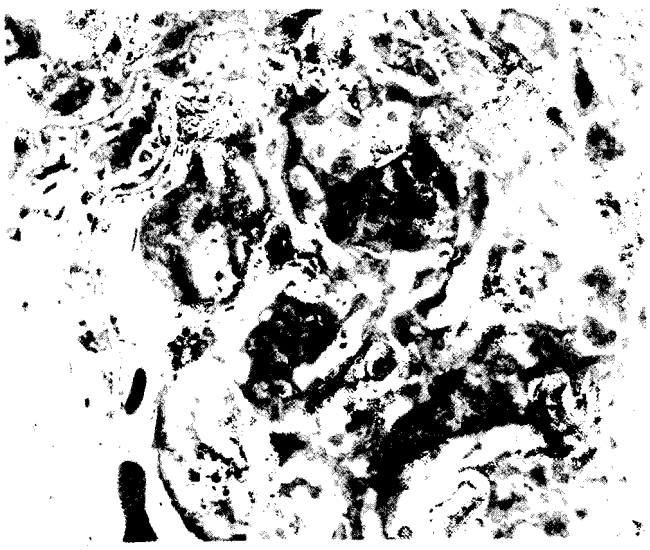

Fig. 3. Glomerulus of APA hamster at 6 months of age. Focal expansion of mesangial region. x 3,540

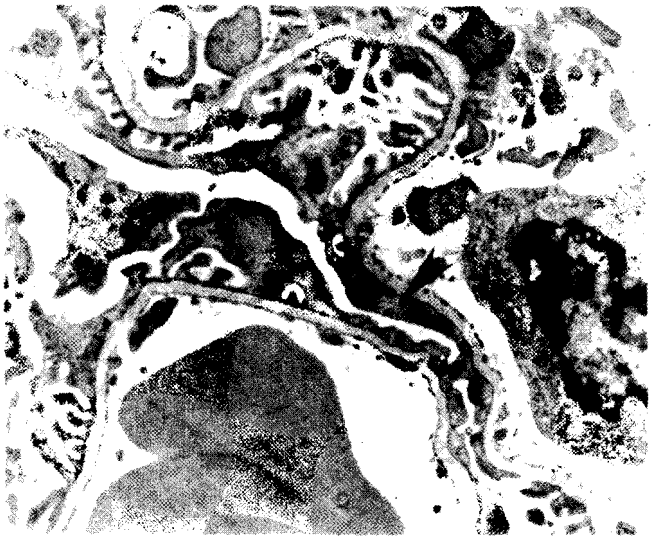

Fig. 4. Glomerulus of APA hamster at 6 months of age. Partial effacement of foot processes of podocytes (arrowhead). x 7,000

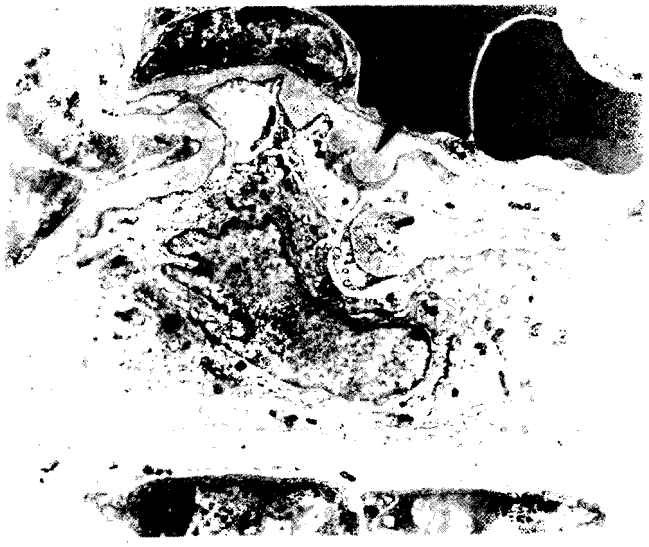

Fig. 5. Glomerulus of APA hamster at 12 months of age. Prominent segmental thickening of capillary basement membrane (arrowhead) and mild dilatation of rough endoplasmic reticula in podocyte. x 4,370

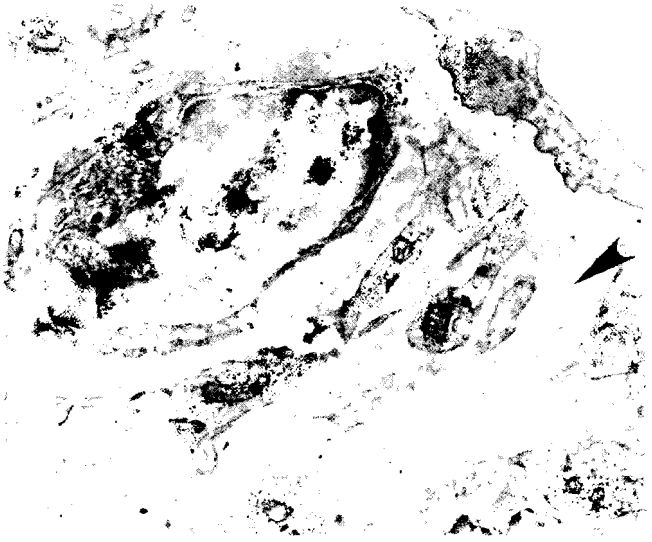

Fig. 6. Glomerulus of APA hamster at 12 months of age. Lipid deposition in mesangial region (arrowhead). x 7,870

lipid deposition occurred in the mesangial region and migration of a part of mesangial cell cytoplasm brought about the thickening of capillary basement membrane. In addition, such an interesting finding as occasional protrusion of a part of the mesangial cell cytoplasm into the capillary lumen was also pointed out. However, the most conspicuous changes were found in podocytes. In podocytes, besides an effacement of their foot processes, various degenerative changes were frequently detected.

The above-mentioned ultrastructural findings suggest that spontaneous glomerular lesions in APA hamsters may develop in mesangium first and then extend to capillary basement membrane and podocytes. Furthermore, as Carroll et al. (1974) discussed in the case of chemically-induced glomerular lesions in rats, severe alterations in podocytes seem to indicate an initiation of irreversible damage in renal glomeruli. As cited above, it was reported that glomerular lesions in APA hamsters indeed progressed quickly after 12 months of age (Doi et al., 1987).

Coinciding with the previous histochemical findings (Doi et al., 1987), no amyloid fibrils were found electron

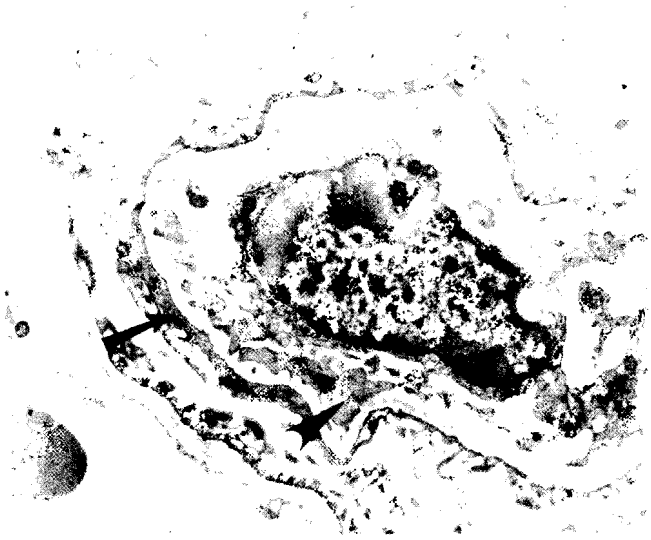

Fig. 7. Glomerulus of APA hamster at 12 months of age. Migration of a part of mesangial cell cytoplasm into capillary basement membrane (arrowhead) and marked effacement of foot processes of podocytes (arrow). x 5,630

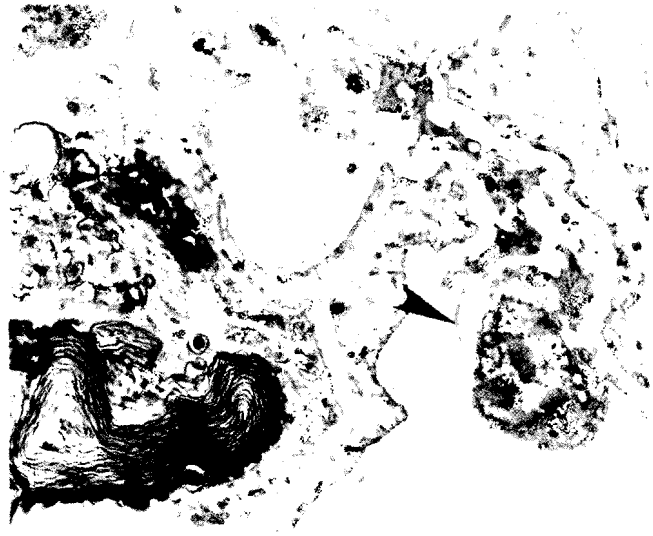

Fig. 8. Glomerulus of APA hamster at 12 months of age. Formation of myelin figures in podocyte and protrusion of a part of mesangial cell cytoplasm into capillary lumen (arrowhead). x 4,360

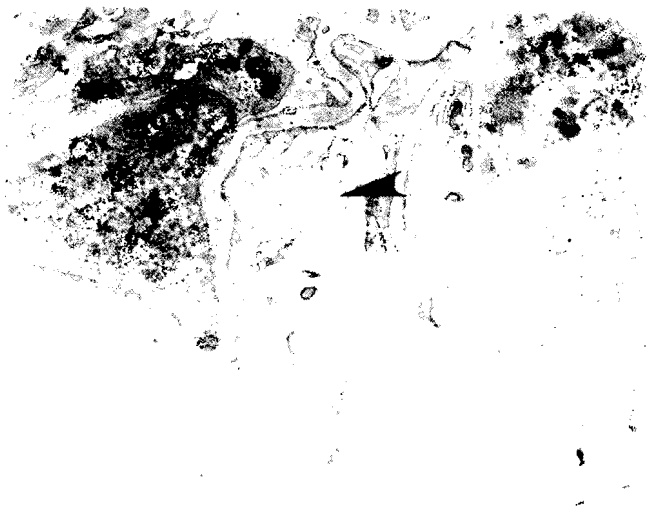

Fig. 9. Glomerulus of APA hamster at 12 months of age. Prominent vacuolization of podocyte (arrowhead). x 5,290

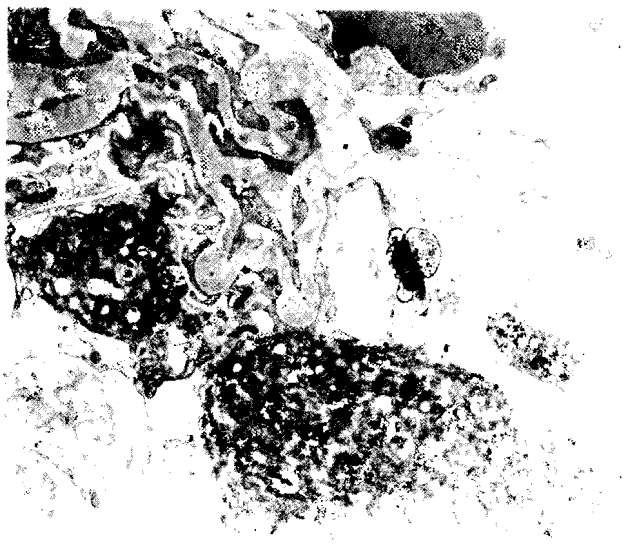

Fig. 10. Glomerulus of APA hamster at 12 months of age. Disappearance of normal cytoplasmic structure of podocyte (arrowhead). x 5,780

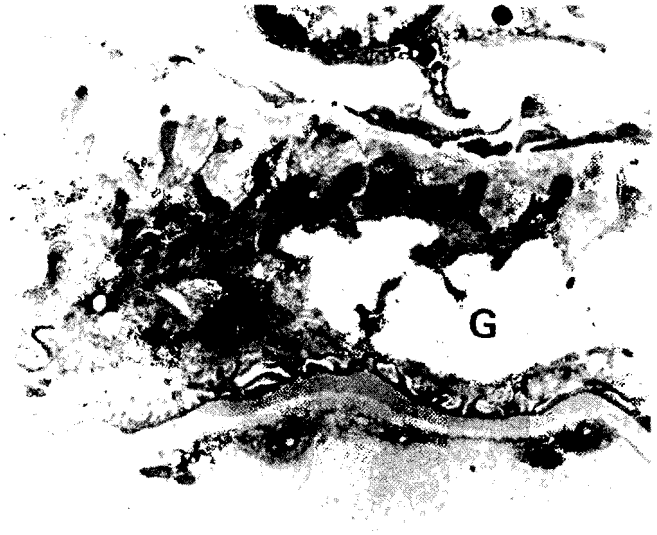

Fig. 11. Wall of Bowman's capsule of APA hamster at 12 months of age. Marked thickening of basement membrane and an accumulation of glycogen granules (G) in epithelial cell cytoplasm. x 5,130

microscopically in any portion of the glomeruli even in 12-month-old APA hamsters. Spontaneous development of FSG with no amyloidosis seems to be one of the characteristics of APA hamsters.

In conclusion, APA hamsters are considered to be a useful tool for the investigation of the development of FSG.

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