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So-called embryonal hyperplasia of Bowman's capsular epithelium:

An immunohistochemical and ultrastructural study

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Summary. The so-called embryonal hyperplasia of Bowman's capsular epithelium (EHBCE) is a rather specific lesion occurring in kidneys of patients maintained on chronic dialysis. It consists of poorly differentiated cells proliferating around sclerosed or obsolescent glomeruli. In this study, immunohistochemical and ultrastructural characterization of EHBCE was performed. The poorly differentiated cells in the lesion exhibited a positive reaction for vimentin and a negative one for cytokeratin (PKK 1) and epithelial membrane antigen. On ultrastructural examination, specialized junctions between adjoining cells, microvilli-like structures on their surfaces, and immature basal folds were observed. These observations suggest that the cells of EHBCE may be associated with the anlage of glomerular epithelium. The background in which neoplasms like renal cell carcinoma or atypical epithelium of cyst wall develop in end-stage kidneys of adult patients on long-term dialysis may cause such a proliferation of poorly differentiated cells in young or paediatric age group patients.

Key words: End-stage kidney – Dialysis – Embryonal hyperplasia of Bowman's capsular epithelium

Introduction

The number of patients on long-term dialysis is increasing, and the occurrence of neoplasms in their kidneys is an important problem from the prognostic point of view (Hughson et al. 1986). Apart from renal cell carcinoma, it has been reported that kidneys of patients on dialysis often exhibit proliferative lesions including proliferations of smooth muscle cells of vessels (McManus et al. 1977), atypical epithelium in the cysts (Hughson et al. 1980), and unusual epithelial proliferation in association with nerves and vessels (McManus and Hughson 1979; McManus et al. 1980). Embryonal hyperplasia of Bowman's capsular epithelium (EHBCE), first described by Hughson et al. (1978), seems specific to kidneys of patients on dialysis. The purpose of this study is to examine the histogenetic origin of EHBCE using immunohistochemical and ultrastructural characterization.

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Materials and methods

A male infant presented with haematuria and proteinuria at the age of 4 years. Renal function deteriorated thereafter, and renal biopsy, performed 8 months after onset, revealed an end-stage kidney. After 4 months, continuous ambulatory peritoneal dialysis (CAPD) was initiated (blood urea nitrogen, 80; serum creatinine, 8.0 mg/dl). He was maintained on CAPD for 12 months, and bilateral nephrectomy was performed in advance of renal transplantation in Tokyo Metropolitan Children's Hospital.

The study was performed on the kidney removed from this patient. The surgical specimen was fixed in 10% buffered neutral formalin, with a portion spared for fixation in 2% glutaraldehyde solution. The former was embedded in paraffin and sliced for haematoxylin-eosin (H&E) staining and staining by the periodic acid-Schiff (PAS) method. Immunohistochemical study employing the avidin-biotin complex (ABC) immunoperoxidase procedure was also performed on the paraffin-embedded tissues. Anti-vimentin (1:20 dilution), anti-epithelial membrane antigen (anti-EMA; 1:100 dilution) antibodies (obtained from DAKOPATTS, Denmark), and anti-cytokeratin antibody (PKK1; 1:100 dilution; obtained from Labsystems, Finland) were applied for the immunohistochemical study. Normal tissue from the adult kidney, removed because of renal cell carcinoma, and fetal kidney, obtained from an autopsied fetus of 20 weeks' gestation, were employed as control specimens for the immunohistochemical study. The specimen fixed in 2% glutaraldehyde solution was postfixed in 1% phosphate-buffered osmium tetroxide and processed for electron microscopy by the conventional method. Thin sections, doubly stained with uranyl acetate and lead citrate, were examined.

Results

Macroscopically, there were no notable changes in the kidney other than marked atrophy. Microscopically, hardly any functioning nephrons were observed. The

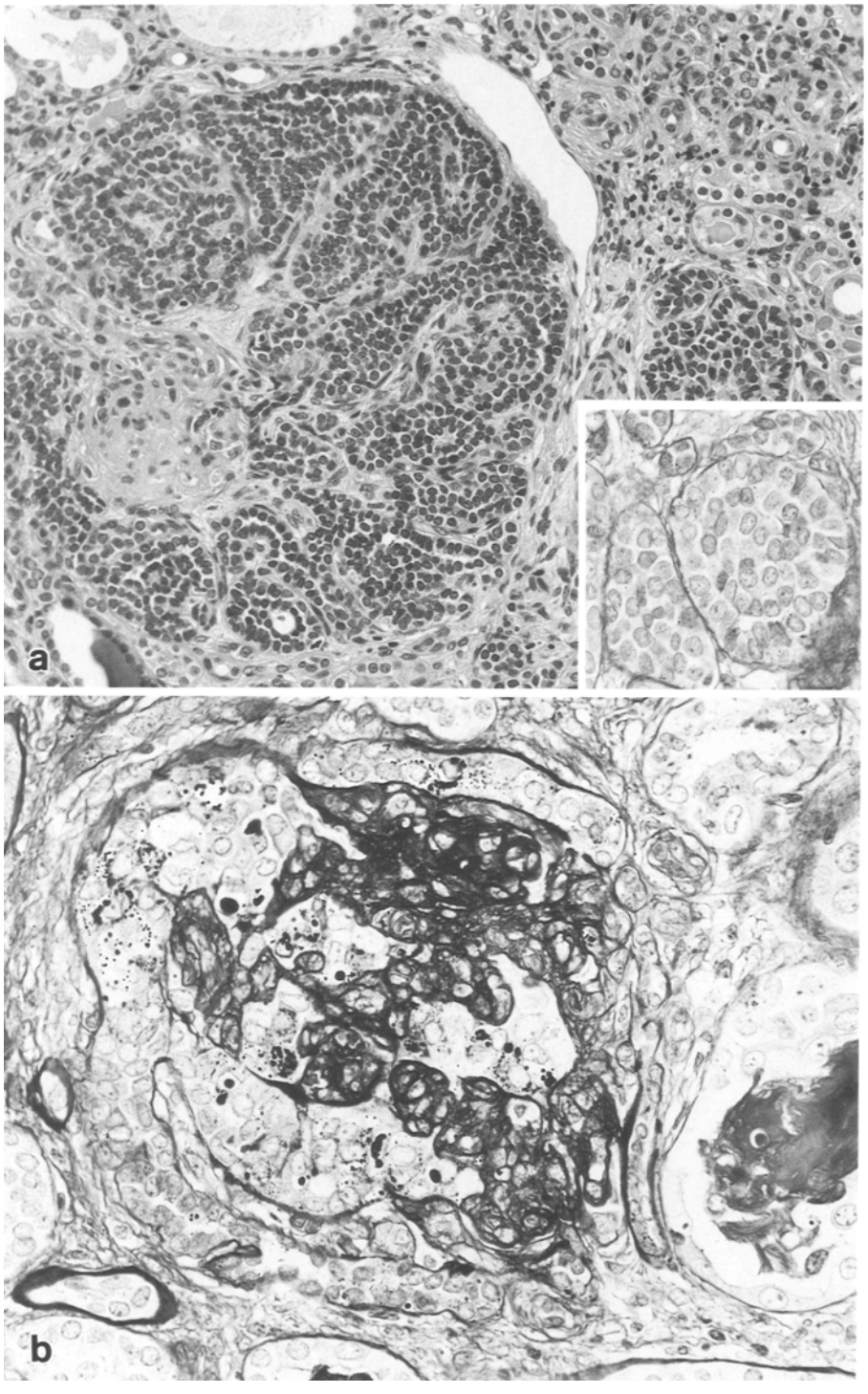

Fig. 1. A Small cells with a round, uniform nucleus and inconspicuous cytoplasm are proliferating around the sclerosed glomerulus. The papillary structure and ribbon-like arrangement are observed. Basement membrane surrounds the small cell nests. H&E, ×200; *inset*: PAS, ×400. **B** The cells proliferating around obsolescent glomerulus are generally confined within Bowman's capsule. PAS, ×400

most remarkable change was EHBCE (Fig. 1A). Small undifferentiated cells with a round, hyperchromatic nucleus and inconspicuous cytoplasm proliferated to form clusters around obsolescent or solidified glomeruli (Fig. 1A). In the clusters, a papillary or tubular arrangement of cells was recognized. Basement membrane could be demonstrated by PAS stain, which surrounded the tubular structures or cell nests (Fig. 1A). Undifferentiated cells were mostly restricted within Bowman's parietal wall (Fig. 1B), but sometimes proliferated over the basement membrane of the parietal wall. Mitotic figures were few in number.

In control material of adult kidney, EMA was detected on the apical membrane of distal tubules and collecting ducts, and on the cell membranes of urothelium. Cytokeratin was manifested in the cytoplasm of distal and collecting tubular epithelium. Epithelia of the proximal convoluted tubules and parietal walls of Bowman's capsule revealed cytoplasmic localization focally. Anti-cytokeratin antibody was not positive in visceral glomer-

ular epithelium. Anti-vimentin antibody reacted strongly with visceral glomerular epithelium and with the endothelium of vessels, smooth muscle cells of arteries and veins, interstitial fibroblasts and macrophages, and Schwann cells of peripheral nerves. Parietal glomerular epithelial cells were focally and slightly positive. In the developing nephrons of fetal kidney, EMA and cytokeratin were positive on the epithelium of the ingrowing ureteric bud and on the urothelium. EMA was not detected at any stage in the developing glomerulus, but cytokeratin was positive in Bowman's parietal epithelium of the immature glomerulus. In the S-shaped vesicle, the localization of cytokeratin was difficult to evaluate. Vimentin staining was manifest focally in the epithelium of the ingrowing ureteric bud. In the developing glomerulus, it was focally positive on both Bowman's parietal and visceral epithelium of glomerulus of developing capillary loop stage, and particularly positive on the latter of rather matured glomerulus. On the epithelium of both the inner and outer layer of the lower limb of the S-shaped vesicle, vimentin was detected focally.

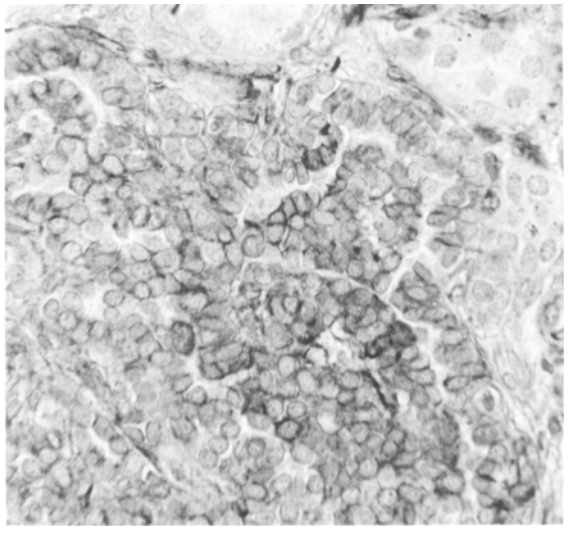

Fig. 2. Positive immunohistochemical reaction for vimentin of embryonal hyperplasia of Bowman's capsular epithelium. ×400

In the present case, anti-vimentin antibody stained the cells of EHBCE (Fig. 2). Neitheir of the other antibodies stained them.

In electron microscopy compact nests of polygonal cells with high N/C ratios were surrounded by basal lamina (Fig. 3A). Each cell had mitochondria and rough endoplasmic reticulum, and lipid droplets were sometimes found. There were desmosomes between cell membranes facing each other (Fig. 3C), and microvilli-like structures were seen (Fig. 3A). There were structures with broad processes on the site facing the basal lamina (Fig. 3B).

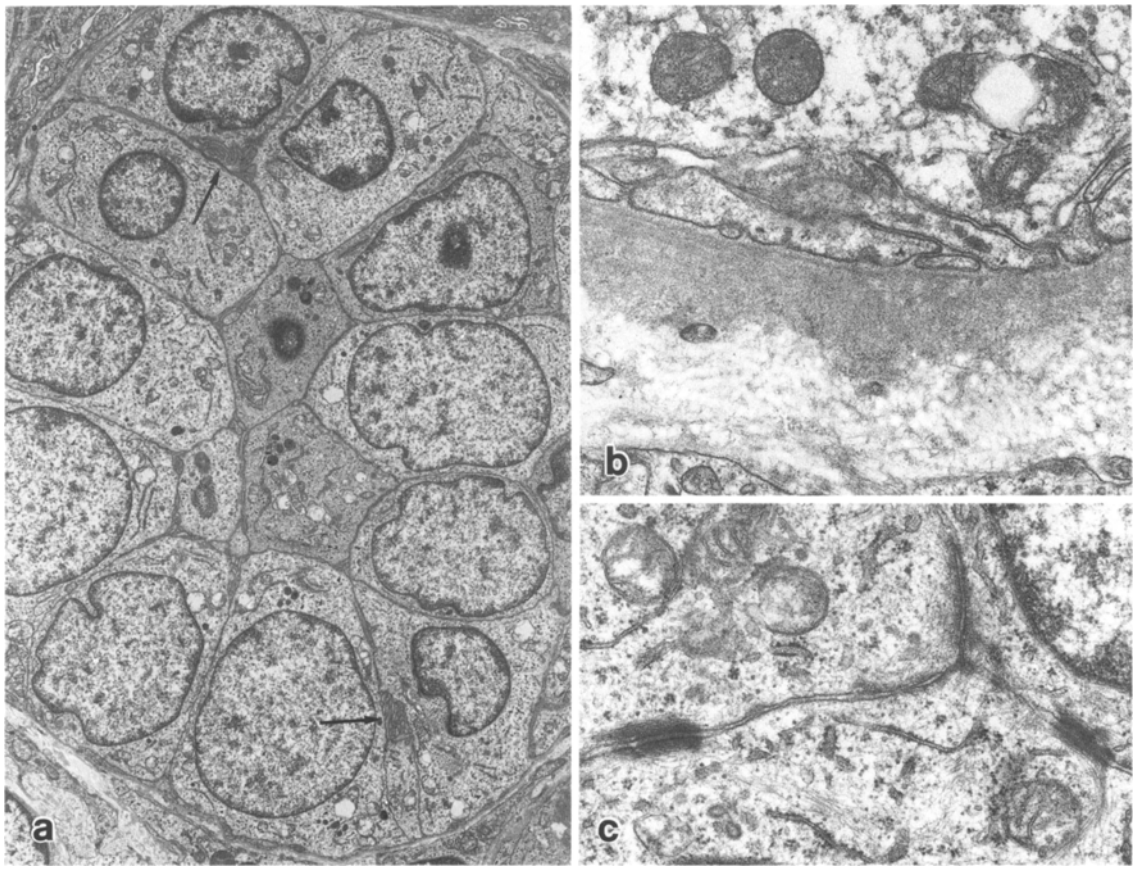

Fig. 3. A Oval or polygonal cells with a high N/C ratio form a cell nest surrounded by basement membrane. There are microvilli-like structures in the intercellular space (*arrows*). ×3500. **B** Cytoplasmic processes are found on the site facing the basal lamina. ×21000. **C** Desmosomes are apparent between the adjoining cells. ×21000

Discussion

EHBCE was first described by Hughson et al. (1978) and was regarded as a dialysis-related epithelial proliferation by McManus et al. (1980). Morphologically, it is a cluster of rather poorly differentiated epithelium proliferating in association with sclerosed glomeruli. It has been suggested that the cell cluster arises from the parietal epithelium of Bowman's capsule (Hughson et al. 1978). In the present study, immunohistochemical and ultrastructural characterization was performed, in an attempt to determine the histogenic origin of the lesion.

An immunohistochemical study of the expression of vimentin and cytokeratin in developing and adult human kidneys was performed by Holthöfer et al. (1984). According to these authors, vimentin was positive in visceral epithelium of the developing and the mature glomerulus. They reported that cytokeratin, while not expressed in glomerular epithelium in either the developing or the adult stage, was positive in Bowman's parietal epithelium and tubular epithelium. According to Fleming and Symes (1987) cytokeratin was demonstrated in the cells of both the glomerular pole and the tubular pole in the S-shaped tubule stage in the fetal kidney, but could no longer be demonstrated in the visceral epithelium of the glomerulus when it became flattened. Fleming et al. (1985) demonstrated that EMA was positive only on the cell surfaces of distal and collecting tubules in adult kidney, and of their embryological precursors. In the present study, poorly differentiated cells exhibited a positive immunohistochemical reaction only to anti-vimentin antibody.

Ultrastructural observations of embryogenesis or differentiation of the glomerulus have been performed. Although there is much controversy as to the origin of endothelium of glomerulus, it has been generally agreed that the precursor of glomerular epithelium is the inner layer cell of the metanephrogenic vesicle (Suzuki 1959) or the upper layer cell of the lower limb of the S-shaped vesicle (Zamboni et al. 1968). Reeves et al. (1978) described the occluding junction of glomerular epithelium and its migration from the apex of cells to their base. Bernstein et al. (1981) demonstrated, in their metanephric cultures, the glomerular differentiation of a bilaminar disc of the S-shaped loop and epithelial differentiation accompanied by occluding intercellular junctions in the columnar cells of the inner lamina of bilaminar disc, and foot process formation apposed to the basal lamina was described. In our case, junctional devices, basal folds and microvilli-like structures projecting into the intercellular or surrounding space were observed.

From the immunohistochemical and ultrastructural investigation in this study, we suggest that the poorly differentiated cells that proliferate around obsolescent glomeruli in end-stage kidneys of a patient on chronic dialysis are associated, in terms of their origin, with poorly differentiated glomerular epithelium.

The development of neoplasms and proliferation of atypical cells in kidneys of patients on long-term dialysis has been reported since Dunnill et al. (1977) first described tumour formation in cystic kidneys in patients undergoing long-term haemodialysis. There have been, however, few reports on EHBCE. In our recent study, in which kidneys removed from 58 paediatric patients on dialysis at renal transplantation were studied morphologically, EHBCE was found in about one-third (Ogata 1990). Leichter et al. (1988) reported that 15 of 42 paediatric patients maintained on dialysis for more than 2 years developed acquired polycystic kidney disease and 1 of them developed neoplastic tubular changes: small cells with hyperchromatic nuclei forming tubules with micropapillae extending into the lumina. It is not clear whether this is a neoplastic change, and whether that pattern of proliferation of poorly differentiated epithelium is the same as those in the present study.

Immunosuppression due to prolonged uraemia (Matas et al. 1975), or polyamines retained in the uraemic stage (Bagrade et al. 1979) may play an important role in developing tumours or atypical cell proliferation. Although further study is required to elucidate what causes the unusual cell proliferation in kidneys of dialysed patients, the background in which neoplasms develop in adult patients could yield the proliferation of poorly differentiated cells in young or paediatric patients on chronic dialysis.

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