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Human cystic kidney diseases: epithelial hyperplasia in the pathogenesis of cysts and tumors

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Abstract. Several examples of human renal cystic disease are associated with tubular epithelial hyperplasia. Micropapillary hyperplasia occurs in autosomal dominant polycystic kidney disease, in localized cystic disease, and in acquired cystic disease; neoplastic or severely dysplastic epithelial hyperplasia occurs in von Hippel-Lindau disease; a histopathologically distinctive epithelial hyperplasia occurs in tuberous sclerosis. In all of these conditions the epithelial hyperplasia appears to be responsible for cyst formation by causing tubular or ductal luminal obstruction, and in all of these conditions, save localized cystic disease (a rare condition with very few reported cases), epithelial hyperplasia imposes an increased risk of malignancy. The risk seems to be highest in patients under treatment with long-term hemodialysis for end-stage kidney disease. Some of these diseases may share common features, but it appears likely that the histopathological differences reflect different features converging on a common result.

Key words: Polycystic kidney disease – Renal carcinoma – Tuberous sclerosis – von Hippel-Lindau disease – Acquired renal cystic disease

Introduction

Recent studies of human polycystic kidney disease (PCKD) have rediscovered epithelial hyperplasia and led to the suggestion that it is responsible for luminal obstruction and the development of cysts [1, 2]. Current interest stems from the observation by Evan and Gardner [3] that small intratubular polyps result from epithelial hyperplasia in the experimental renal cystic disease induced by diphenylamine. Evan et al [4] showed similar micropapillary epithelial hyperplasia in human "adult" autosomal dominant PCKD and suggested that epithelial hyperplasia was the primary pathogenic event. Epithelial hyperplasia is common to other forms of human renal cystic disease, both congenital and acquired [5], in which hyperplasia may be responsible for both cyst formation and an increased risk of malignant degeneration.

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Autosomal dominant polycystic kidney disease

Uneven and irregularly distributed micropapillary epithelial hyperplasia in autosomal dominant polycystic kidney disease (AD-PCKD) results in intraluminal projections of seemingly piled up cells and micropolyps (Fig. 1). The abnormality, occurring in minimally dilated ducts as well as in gross cysts, appears to have preceded cyst formation. The unevenness of the hyperplasia indicates that not all tubules are equally affected. Scanning electron microscopy [4] has shown some cysts to be studded with micropolyps and others to contain polyps at their narrow distal ends, where they seemed to obstruct the lumen.

Only a small proportion of nephrons are likely to be affected in AD-PCKD [5, 6], possibly because of nephron diversity resulting from both genetic and local influences. Progression to renal insufficiency probably depends on nephron loss from the compression of adjacent parenchyma rather than on recruitment of new cystic nephrons. Localization of the abnormality to a minori-

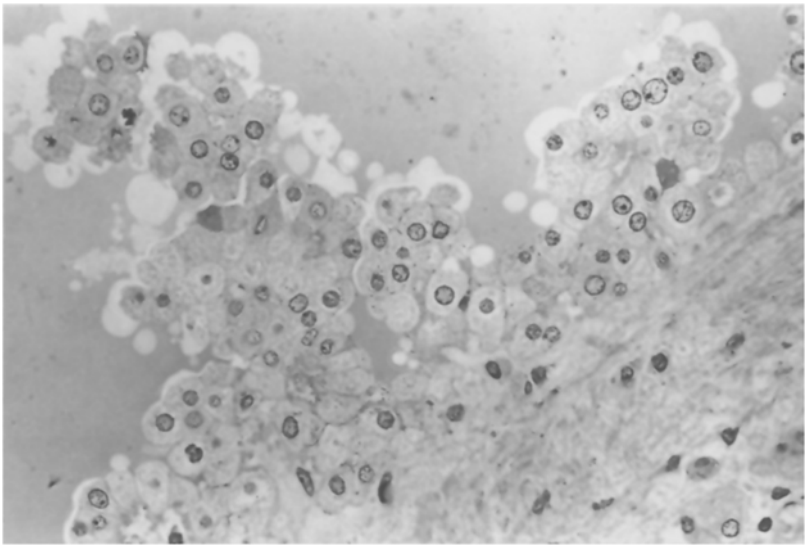

Fig. 1. Epithelial hyperplasia in autosomal dominant polycystic kidney disease. The epithelial cells lining the cysts are hyperplastic and piled into a nonvascularized micropolyp. Azure II-methylene blue stain, ×300.

ty of nephrons and to segments of those nephrons does not contradict the genetic basis of the disease, as it is clear from the abundant evidence of morphological and functional heterogeneity that different segments of the nephron operate under different genetic controls. Localization of the cysts may occur in segments that have relatively more compliant walls and that dilate preferentially in response to distal obstruction; however, tubular basement membranes in AD-PCKD are usually thicker than normal and cannot be demonstrated to have greater than normal compliance [7].

Epithelial hyperplasia in AD-PCKD has sometimes been regarded as neoplastic, an interpretation that goes back to the beginning of the century. Although the risk of malignancy is not known, the rate of neoplasia in AD-PCKD is higher than in the general population. Bilaterality is present in 20% of AD-PCKD related tumors, but appears in less than 5% of renal tumors not related to AD-PCKD [8]. Rather than regarding the entire process as essentially neoplastic, we think that epithelial hyperplasia in AD-PCKD carries the potential for neoplastic transformation, with a risk of malignant degeneration.

von Hippel-Lindau disease

The interpretation of neoplasia in cystic kidneys is obscured somewhat by the well-known occurrence of both cysts and tumors in von Hippel-Lindau disease, which comprises renal cysts and carcinomas, cerebellar and retinal hemangioblastomas, pancreatic cysts and adenomas, and epididymal cystadenomas. Although most patients with von Hippel-Lindau disease have less than severe renal cystic disease, renal involvement grossly indistinguishable from AD-PCKD has occasionally been reported [9, 10]. The occurrence in a young patient of multiple hypernephromas or of hypernephromas arising in cysts should prompt a search for other manifestations of the syndrome. As many as 15 tumors in one patient have been reported [11].

Although cysts are often described as being lined with flattened, nondescript epithelium, it is usually irregularly hyperplastic, with mural nodules of clear cell carcinoma [11, 12] (Fig. 2). We believe the cysts and tumors to be related, therefore, and the hyperplastic and nodular epithelial lining to be both the cause of tubular obstruction and the direct precursor of malignancy.

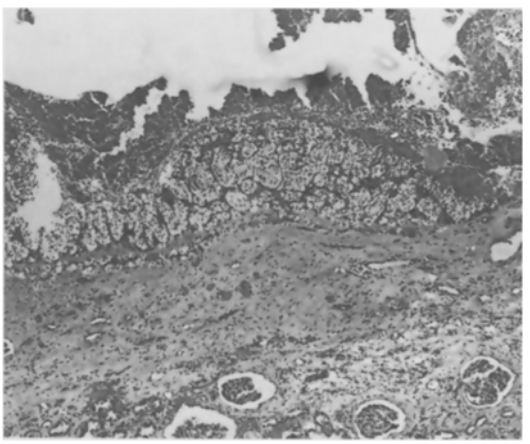

Fig. 2. Malignant transformation in von Hippel-Lindau disease. The cyst contains a mural nodule of clear-cell carcinoma. H & E stain, ×40

Tuberous sclerosis

Renal cysts in tuberous sclerosis are lined with distinctive epithelium, possibly unique to this condition [13]. Renal biopsy may be diagnostic, even when the clinical features of the disease are not immediately apparent. The distinctive feature of the cysts is the striking hyperplasia of their epithelia. They are lined with large eosinophilic epithelial cells, and the epithelial hyperplasia appears to be responsible for both cyst formation and an increased risk of renal cell carcinoma. Although fewer than a dozen well-documented cases have been reported, at least four patients have had bilateral tumors, and as many as six separate tumors have occurred in one kidney. These tumors are to be differentiated from angiomyolipomas, which are nonepithelial renal tumors that also occur with increased frequency in tuberous sclerosis.

Cystic disease in tuberous sclerosis can lead to chronic renal insufficiency. Patients in chronic renal failure have had cystic disease and multiple tumors together, the tumors including both angiomyolipomas and renal carcinoma.

Acquired renal cystic disease

The occurrence of renal cysts in end-stage kidneys has received great attention since its initial description by Dunnill et al. [14] in 1977. The phenomenon has now been described in over 400 patients [15–19]. There seems to be general agreement that acquired cystic disease develops in approximately 40% of patients treated with hemodialysis for periods longer than 3 years, although the interval need not be that long. Dunnill et al. [14] recognized that these patients also develop multiple renal tumors, as confirmed by more recent studies [15, 18, 19].

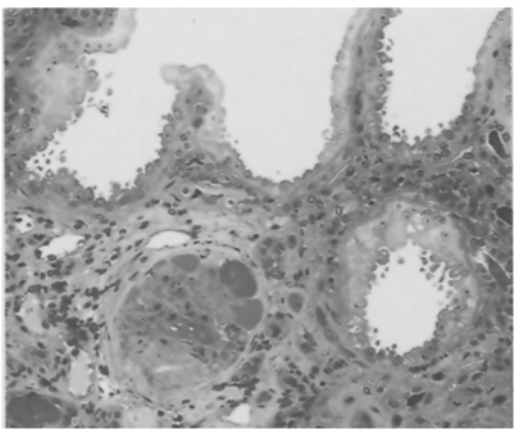

Fig. 3. Epithelial hyperplasia in acquired cystic disease. Dilated tubules are lined with piled-up, large epithelial cells. H & E stain, ×40

The cysts and tumors are related to each other through epithelial hyperplasia (Fig. 3). The cysts bear a strong, but possibly not a necessary association with hemodialysis. Acquired cystic disease may be prevented or retarded by renal allotransplantation. Almost all histopathological studies have shown the cysts to be lined with hyperplastic and atypical or dysplastic epithelium, forming micropapillae and small intraluminal tumors.

Although renal tumors develop in noncystic kidneys, their frequency is increased in patients with acquired cystic disease. Tumors of all types – adenomas and carcinomas – occur in about 20% of patients with acquired cystic disease, slightly less than 10% of long-term dialysis patients. About one-fourth of the tumors have been malignant on histopathological grounds, and a small proportion of the histopathologically malignant tumors has been clinically malignant, with metastases and death. Evan and Gardner [15] used published data to calculate the risk of renal adenocarcinoma among dialysis patients. The incidence was 6 per 1,000 among all dialysis patients, and it increased to 45.5 per 1,000 in those with acquired cystic disease. The frequency of acquired cystic disease increases with the duration of hemodialysis, but the frequency of acquired cystic disease, as a percentage of all patients, varies greatly from one clinical unit to another. The reasons for the variations are unexplained, perhaps reflecting differences in duration of dialysis, interest and awareness of physicians, diagnostic techniques and criteria, and dialysis techniques themselves. It is important to determine why some nephrologists, despite accumulating data, persistently describe their failure to identify acquired cystic disease and tumors among their dialysis patients.

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