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Multilocular Renal Cyst

Case Report, Ultrastructure and Review of the Literature

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Summary. Multilocular renal cyst is an uncommon focal, unilateral, cystic, epithelial lesion of uncertain pathogenesis. Because nephroblastomatous foci have been found on microscopic examination of several of the reported cases, some authors have proposed that multilocular cysts are differentiated and cystic forms of Wilms' tumour. This proposition is analysed and it is concluded that three possibly interrelated lesions may be defined: (1) Wilms' tumours showing cystic differentiation. (2) Lesions macroscopically indistinguishable from multilocular cyst containing variably differentiated nephroblastomatous foci. All such cases have been described in infants. (3) Typical multilocular renal cysts, which have described in children and adults. Review of the literature shows that several cases have been included in the second category solely because of the presence of small intraseptal tubules. Consequent anomalies of interpretation are highlighted and a further case of multilocular cyst in an adult female is reported in which ultrastructural examination, recorded for the first time, confirms the epithelial nature of the cyst lining cells which resemble simplified renal tubular epithelium.

Key words: Kidney, cystic – Multilocular renal cyst – Nephroblastoma.

Introduction

Multilocular renal cyst is a focal, unilateral, cystic epithelial lesion occurring in all age groups. The lesion is non familial and is not associated with cystic changes in other organs. Criteria for the diagnosis are established (Powell et al., 1951; Boggs and Kimmelstiel, 1956). Several theories of pathogenesis have been put forward and controversy surrounds the hypothesis, based on the finding of variably differentiated nephroblastomatous foci in several reported cases,

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that these lesions are the result of differentiation and maturation of Wilms' tumours.

Case Report

A 58 year old female was admitted to hospital with a 2 day history of persistent macroscopic haematuria. There were no other urinary symptoms. Two episodes of cystitis and pyelonephritis had occurred two years before. The blood pressure on admission was 170/90 mm Hg, the urine was bloodstained and a left sided, tender, non ballotable renal mass was palpable. There was no family history of renal disease. The haemoglobin was 11.6 g/100 ml. All other laboratory investigations, including tests of renal function, were normal. Radiological studies, including angiography, demonstrated a large lucent mass in the mid portion of the left kidney with small vessels stretched around its margins. Tiny irregular vessels were seen within the mass but no distinct tumour circulation was demonstrated. Uninvolved kidney appeared normal. Left thoraco-abdominal nephrectomy was performed, the provisional clinical diagnosis being renal cell carcinoma. The patient recovered uneventfully and was discharged ten days after operation. She remains well 4 years later.

Pathologic Findings

The left kidney weighed 1,290 g and measured $22 \times 12 \times 11$ cm. The upper three quarters of the specimen was incompletely replaced by a circumscribed multilocular cystic mass $16 \times 9 \times 8$ cm (Fig. 1). The lesion was bounded by a well developed capsule continuous with the renal capsule and was clearly demarcated from the adjacent renal tissue, which appeared normal although peripherally attenuated over the cystic mass. The lesion was made up of innumerable cystic locules ranging in size from a few millimetres up to 5 cm maximum diameter, separated by thin connective tissue septa. The locules had smooth, glistening linings and contained clear or slightly bloodstained watery fluid. Focal dense calcification was apparent. No solid areas were identified. The locules communicated neither with each other nor with the renal pelvis. A single triple branching renal artery was present and the venous and drainage systems appeared normal.

Microscopic Examination

The lesion was bounded by a dense collagenous capsule. The cysts were supported by connective tissue septa of varying thickness and cellularity (Fig. 2a, b, c), some consisting of dense hyaline collagen, while others had a more cellular fibroblastic character with sporadic looser spindle cell areas. Embryonal or blastemal elements were not seen. Small intercystic tubules, resembling simplified renal tubules, were present infrequently within septa (Fig. 3) in addition to irregular islands of calcification and ossification (Fig. 2d). There were occasional mononuclear inflammatory cells, rare mast cells and sporadic macrophage aggregates. Degenerate areas incorporating cholesterol clefts with associated giant cell formation were also present. The cyst epithelium was generally of cuboidal or low columnar morphology, with areas of marked attenuation and rare foci of nuclear pleomorphism. Scattered cysts were lined by vacuolated epithelium.

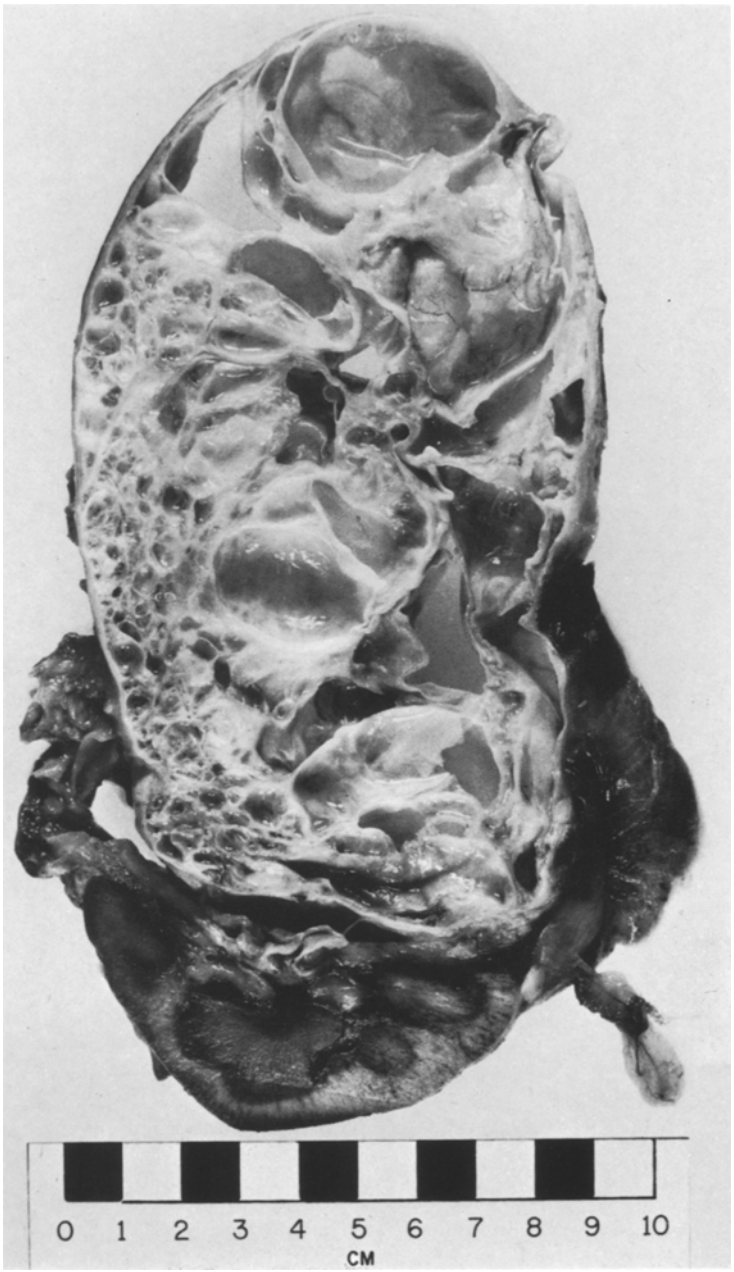

Fig. 1. Section through multilocular cystic lesion and kidney. A well developed capsule surrounds the cyst which is clearly demarcated from the adjacent renal parenchyma

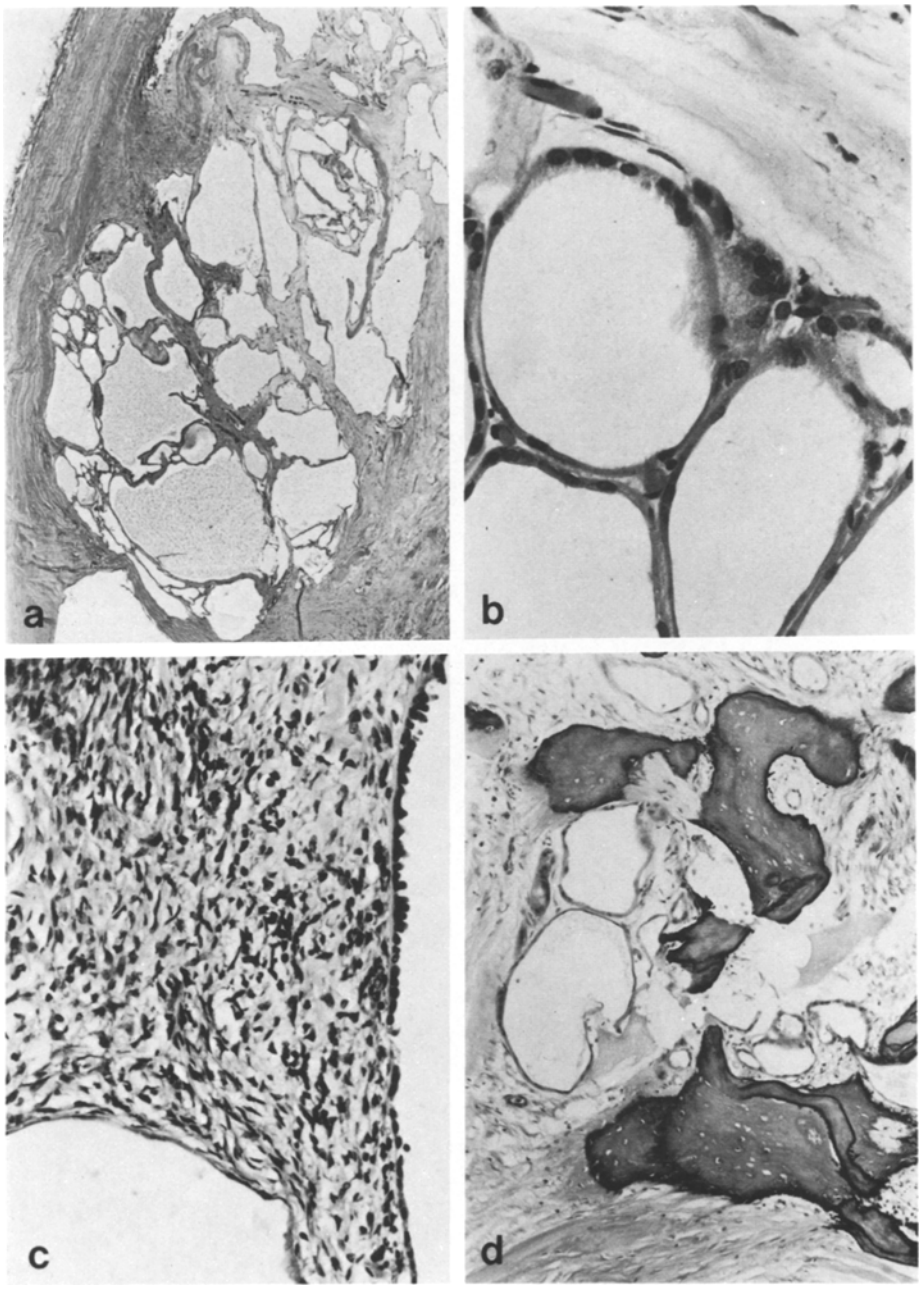

Fig. 2. a Capsular region of cyst. Delicate connective tissue septa separate daughter locules of greatly varying size. H.E. ×20. **b** Low cuboidal epithelium lining several locules. The adjacent stroma is relatively acellular. H.E. ×260. **c** Localised focus of increased stromal cellularity; the epithelium of the larger cyst is mildly pleomorphic. H.E. ×200. **d** Stromal bone formation. H.E. ×80

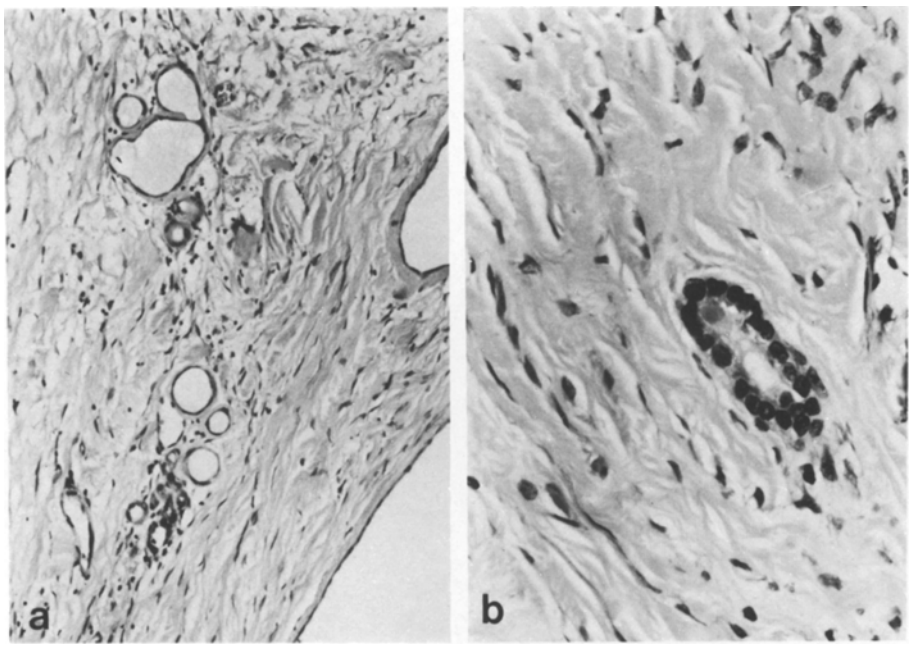

Fig. 3. **a** Clusters of small tubules within a septum separating larger cysts. H.E. ×100. **b** One of several small, isolated intraseptal tubules. H.E. ×320

Great variation in cyst size was a conspicuous feature and some contained proteinaceous material. No glomeruloid structures or heterologous elements were found in sections prepared from 54 tissue blocks. The adjacent kidney showed minor cortical scarring associated with patchy mononuclear inflammatory cell infiltration and sporadic minor cystic dilatation of scattered tubules in both cortex and medulla. Mild arterial intimal fibroelastosis and arteriolar hyalinosis were also present. A perinephric lymph node separately submitted showed follicular hyperplasia.

Electron Microscopy

Tissue selected at random from the cystic interior of the formalin fixed specimen was post fixed in glutaraldehyde and osmium tetroxide, and embedded in epon. Ultrathin sections were prepared from areas including both cyst epithelium and supporting stroma and stained using uranyl acetate and lead citrate.

Ultrastructural examination confirmed the epithelial nature of the cyst lining cells which although variable in height, shared common features (Figs. 4, 5). The nuclei were oval or indented and irregular, with generally dispersed chromatin but often contained scattered small heterochromatin masses. Nucleoli were sporadically seen. The cytoplasm contained variable numbers of organelles-lysosomes, polyribosomes and mitochondria being moderately frequent. Rare

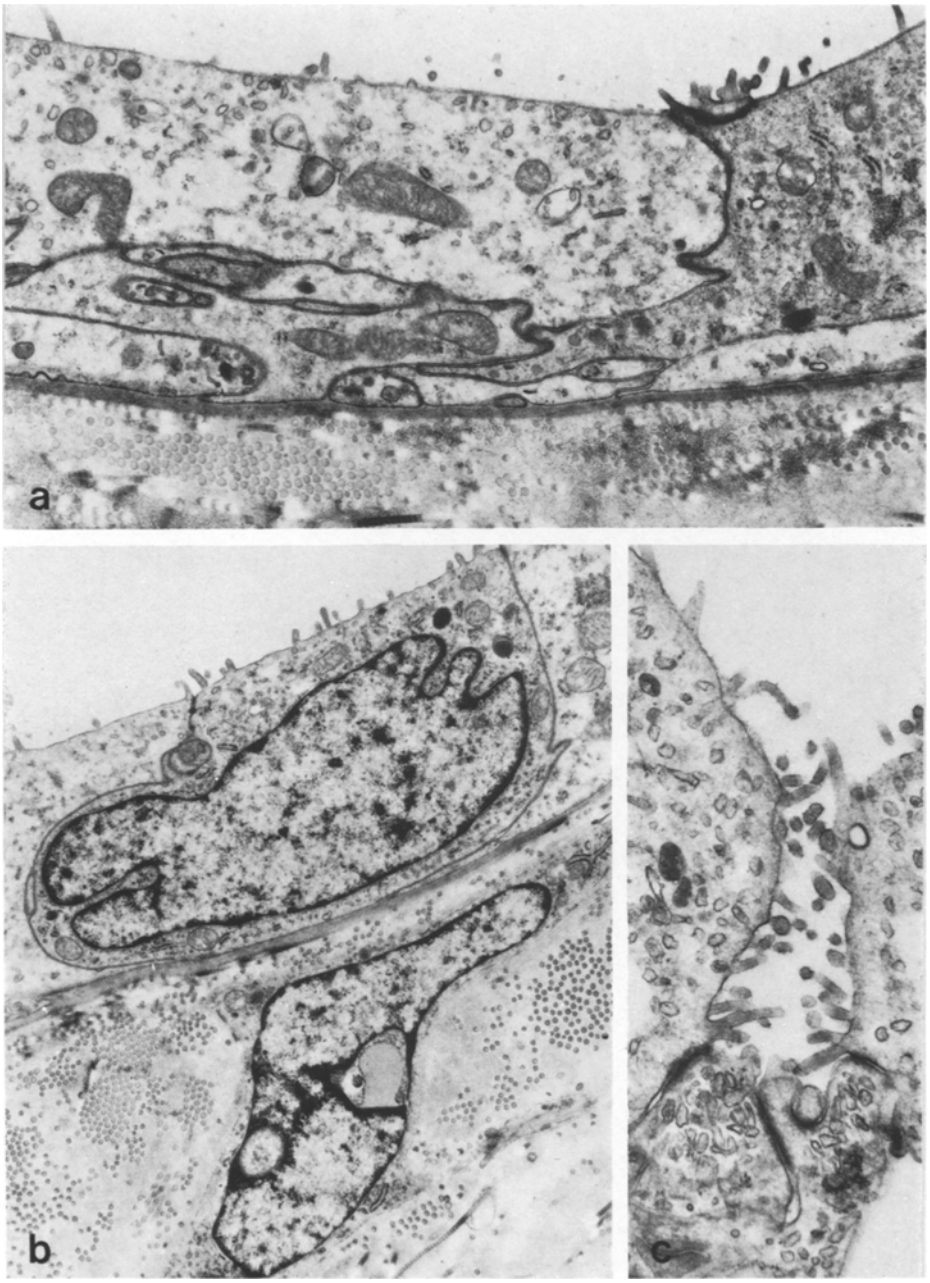

Fig. 4. a Interdigitating cyst lining epithelial cells, adjacent basal lamina and underlying collagenous stroma. A surface junctional complex and short microvilli are evident. EM ×12,500. **b** Cyst lining epithelial cell showing nuclear irregularity. Portion of a fibroblast is present in the underlying stroma. EM ×8,000. **c** Luminal aspect showing junctional complexes and variably developed microvilli. EM ×18,000

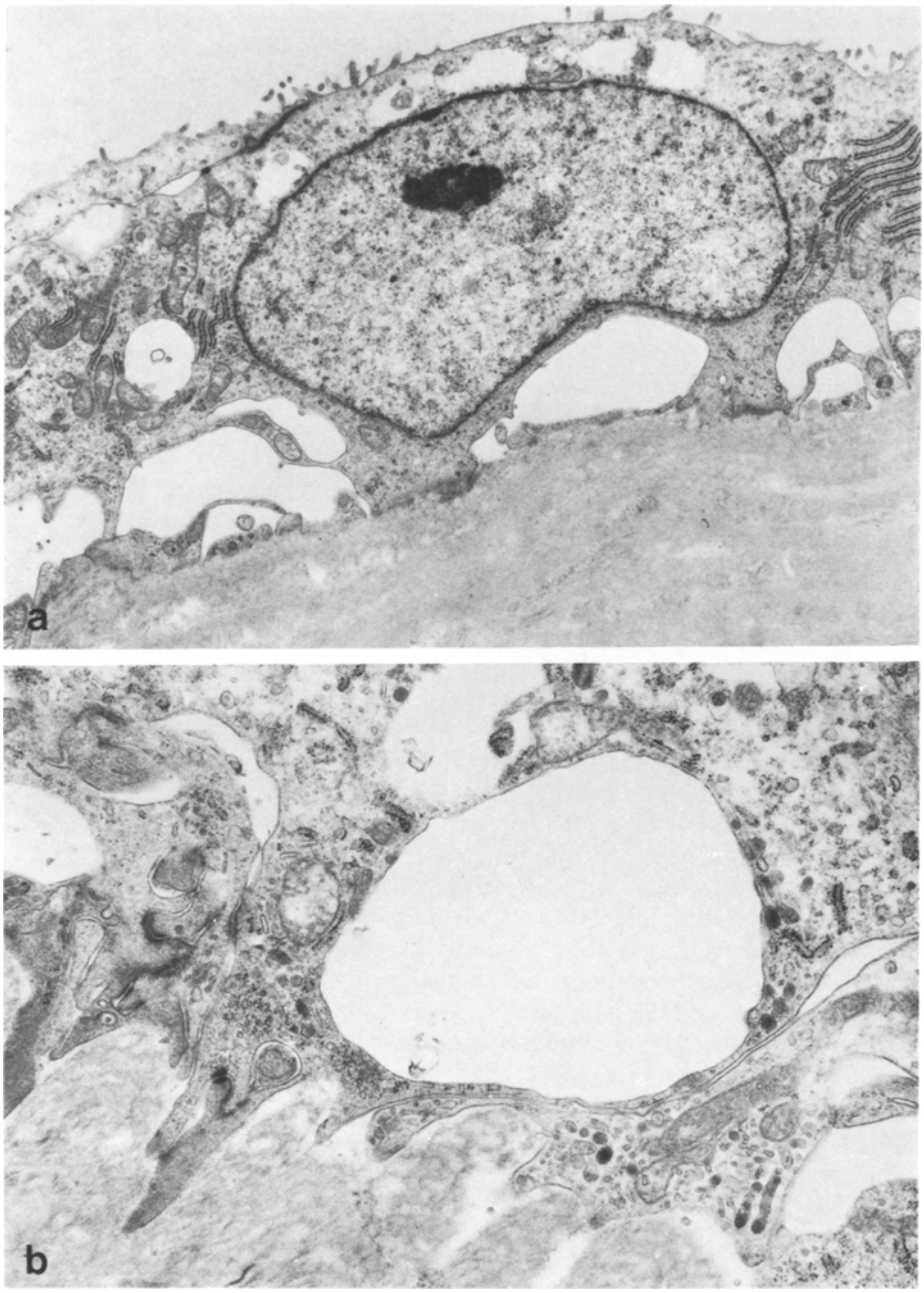

Fig. 5. **a** Cyst lining epithelial cell. The cytoplasm contains scattered mitochondria and stacks of rough endoplasmic reticulum. Expanded intercellular spaces and a greatly thickened basal lamina are also apparent. EM ×7,000. **b** Basal aspect of cyst epithelium showing intercellular spaces and cellular interdigitation with desmosomes. EM ×14,500

autosomes containing myelinoid bodies were noted. Small agranular vesicles or tubules were numerous and rough endoplasmic reticulum was present scattered sparsely throughout the cytoplasm, as short lengths, dilated sacs or small stacks. There were a few fine microfilaments in some cells. Short, variably orientated surface microvilli were common, with conspicuous surface junctional complexes and there were irregularly distributed intercellular spaces. Some cellular interdigitation and scattered desmosomes were seen but basal infoldings of the plasma membranes were not prominent. The basal laminae showed great variation in thickness, being extremely thickened around some cysts, a feature possibly exaggerated by oblique sectioning. The supporting stromal tissues were rather featureless being composed of dense bundles of mature collagen fibrils infrequently interrupted by masses of basement membrane-like material. Scattered fibroblasts and capillaries were evident and a few mast cells were noted.

In general terms, the cyst ultrastructure recapitulated, in simplified form, aspects of normal renal tubular morphology and perhaps most closely resembled the collecting tubule.

Discussion

The literature on multilocular renal cyst has been complicated by controversial terminology, like entities and confusing synonyms. The lesion has been categorised as unilateral multicystic kidney, cystadenoma, lymphangioma, partial or focal polycystic kidney, segmental cystic disease, benign multilocular cystic nephroma and various other titles with nephroblastomatous connotations. Edmunds in 1892, described what is usually accepted as being the first reported case, calling it "cystadenoma of the kidney," although Aterman et al. (1973) noted that earlier workers probably misinterpreted these lesions as lymphangiomas. It was not until 1951 that Powell et al. described 8 criteria for the diagnosis of multilocular renal cyst in an attempt to clearly separate the lesion from other forms of renal cystic disease. The criteria were as follows: (1) The cyst should be unilateral; (2) it should be solitary; (3) it should be multilocular; (4) the cyst should not communicate with the renal pelvis; (5) the loculi should not communicate one with another; (6) there should be a definite epithelial lining to the loculi; (7) there should be no renal elements within the main cyst; (8) if residual kidney tissue is present it should be normal. In 1956, Boggs and Kimmelstiel suggested certain modifications and applied the following criteria: (1) The lesion must be multilocular; (2) the cysts must, for the most part, be lined by epithelium; (3) the cysts must not communicate with the pelvis; (4) the residual renal tissue should be essentially normal, except for pressure atrophy; (5) fully developed, mature nephra or portions of such should not be present within the septa of the cystic lesion. The last criterion recognises that in some cases, variably developed tubular structures are present within septa of multilocular cysts, and that sometimes immature or embryonal elements, including glomeruloid structures, may also be found. Indeed it was the presence of such components which prompted the report of one of their cases. Similar

components have been recognised by others and have led to a controversy over nomenclature and the possible neoplastic nature of the entity.

Reviews of the literature were undertaken by Aterman, Boustani and Gillis (1973), and by Baldauf and Schulz (1976). The combined data which also include 13 cases accepted by Powell (1951), yield 66 cases reported since Edmunds' original case of 1892. Of these 66, 38 were in children and 28 in adults, with an age range from birth to 71 years but with an intriguing and unexplained hiatus between the ages of 5 and 18 years. An approximately equal sex incidence was apparent in the paediatric group (19 males, 17 females of 36 cases in which the sex was specified), but in the adult group, more than twice as many females as males were affected (20 females, 8 males). All cases have been unilateral. Familial cases have never been recorded and apart from the incompletely documented case of Osathanondh and Potter (1964, case 9) with multiple anomalies, and of one other child with a Meckel's diverticulum, no associated congenital lesions have been described – in particular, cysts in other organs have never been recorded. Of 64 cases in the combined series in which the side of the lesion was stated, 30 occurred on the right side and 34 on the left. Baldauf and Schulz also made reference to the Japanese literature (Kawamura and Miyakawa, 1969) in which was described the case of a 5 year old girl, the oldest paediatric case recorded, and the case of a man who had a coexistent renal cell carcinoma with pulmonary metastases. Coexistence with renal cell carcinoma is also recorded in 2 of 10 cases of multilocular cysts by Uson and Melicow (1963), and Pearlman (1964) described a case of adenocarcinoma of the kidney coexistent with a "large multiloculated cyst" which, at least grossly, resembled a multilocular renal cyst.

The characteristics which distinguish other forms of renal cystic disease from multilocular cyst have been comprehensively dealt with by other authors (Boggs and Kimmelstiel, 1956; Arey, 1959; Dainko et al., 1963; Ghosh and Dorfmann, 1972). Attention to the diagnostic criteria reiterated in this paper should enable distinction from polycystic disease, multicystic kidneys, simple cysts, cystic renal cell carcinoma, papillary cystadenoma of the kidney and lymphangioma.

Speculation about the nature and pathogenesis of multilocular renal cysts has revolved around suggestions that the lesions are either neoplastic or the results of developmental errors. Powell (1951) suggested that the lesion developed by distension of embryonically sequestered and persisting tubules but considered the alternative possibility of degenerative processes resulting from ischaemia or obstruction. Multilocular cysts were included by Osathanondh and Potter (1964) in their type 2 group of polycystic kidneys, in which they concluded, (on the basis of microdissection), that the abnormalities result from interference (possibly of environmental origin) with the normal differentiation of the ureteral bud and inhibition of ampullary activity, which prevents nephron induction and causes premature cessation of tubule branching with conversion of ampullary portions of tubules into cysts. Essentially similar appearances were, however, described by these authors in cases of bilateral involvement, cases with major malformations in other organs and cases with diffuse involvement of one kidney (so-called multicystic kidney) as well as in cases typical of multilocular cyst.

The similar microdissection findings in these apparently diverse situations might reflect variation in the degree of organ involvement by a single process, but it is difficult to accept these cases as a homogeneous group. It is none the less clear that morphologically and genetically the multilocular renal cyst, with no familial tendency and no associated hepatic abnormalities is quite distinct from the infantile and the adult types of polycystic disease. It is also pertinent to note that acceptable congenital cases have not been reported and in contrast, several cases are described in old age and two cases are recorded in which the kidneys were apparently normal on excretory urography, 1 year and 4 years before the diagnosis became obvious. (Attwood and Grieve, 1958; Uson and Melicow, 1963).

Multilocular Renal Cyst and Nephroblastoma

Of the two cases reported by Boggs and Kimmelstiel (1956), one (case 1), while macroscopically typical of multilocular cyst, contained foci of "embryonic mesenchyme with frustrated formation of renal tubules and glomerular anlagen". They regarded these areas as "tumorous", representing elements similar to those seen in Wilms' tumour and indicating origin from metanephric blastema. In view of the absence of either clinical or morphologic evidence of malignancy, they designated the lesion "benign, multilocular cystic nephroma" and proposed that all multilocular cysts should be regarded as neoplastic. Earlier, Frazier (1951), had also described a multilocular cyst which contained "rather primitive looking connective tissue" but drew no special conclusions from this observation. Subsequent authors have described further multilocular cysts containing blastemal or embryonal elements (Uson et al., 1960, case 1; Christ, 1968; Landing, 1968; Brown, 1974) variously interpreting this combination as either due to separate though coincident aberrations of blastemal development (Uson et al., 1960) or as being integral parts of a single entity, supporting the notion that multilocular cysts were essentially nephroblastomatous (Christ, 1968; Landing, 1968). Willis (1962) referred to the possibility of maturation occurring in nephroblastoma, converting "most or all of the tumour into well differentiated tubules and cysts, connective or skeletal tissues, and muscle ..." and there is certainly no doubt that cystic change may occur in Wilms' tumours (Uson et al., 1960; Bennington and Beckwith, 1975; Merten et al., 1976; Stambolis, 1978). Brown (1974) coined the name "cystic partially differentiated nephroblastoma", a variation on the previous terms "differentiated nephroblastoma" (Fowler, 1971) and "benign cystic differentiated nephroblastoma" (Lazner and Jureidini, 1971). The two cases described by these authors, in contrast to earlier descriptions, contained no undifferentiated blastema, heterologous mesenchymal elements or organoid structures, although small septal tubules were present which were regarded as embryonal. However the absence of frankly nephroblastomatous elements is a fundamental difference from the other cases delineated above. In other words, the lesions described by Fowler and by Lazner and Jureidini, are indistinguishable from multilocular renal cyst as previously defined by the

criteria of Boggs and Kimmelstiel. This notwithstanding, the authors postulated pathogenetic homogeneity for multilocular cysts and "cystic differentiated nephroblastomas", the observed histological differences being interpreted as only those of maturation and proportion of the various elements. Fowler went so far as to draw an analogy with ganglioneuroma-neuroblastoma, suggesting that every "nephroma" must have once been a nephroblastoma. Aterman et al. (1973) considered such suggestions to be based on unproven assumptions and expressed misgivings about the "embryonic" nature of tubular structures reported in multilocular cysts, pointing out that such tubules were by no means certainly "primitive". Bennington and Beckwith (1975) considered it unlikely that multilocular cysts were neoplastic and related to nephroblastoma because the "relatively high" frequency of non neoplastic congenital urinary tract abnormalities associated with nephroblastoma was not seen in cases of multilocular cyst.

The controversy is current and was compounded rather than resolved by Joshi et al. (1977) who described three more cases, with variably differentiated nephroblastomatous elements, which they also termed "cystic partially differentiated nephroblastoma". In reviewing the previous reports of similar cases, including the cases of Fowler, and Lazner and Jureidini, they added the second case of Uson et al. (1960) despite the fact that the gross lesion in this case consisted of multiple cysts in association with Wilms' tumour without the configuration of a multilocular cyst. Further they included the case of Dainko et al. (1963), asserting that those authors described embryonic renal elements in the septa of the lesion, a somewhat fanciful interpretation of what was in fact described as "tubular and glomerular remnants ... recognisable between some loculi immediately adjacent to the dense fibrous connective tissue capsule". Dainko and his associates interpreted this lesion as a multilocular cyst. Despite this and in a curious reversal of the trend, Joshi et al. claimed that all of the cases discussed represented the result of differentiation of nephroblastomas and categorically separated them from multilocular cyst. The authors used as the criterion to distinguish "cystic partially differentiated nephroblastoma", "the presence of partially or well differentiated renal elements or renal blastema cells in the septa of the locules of the cyst". In using only Powell's criteria for the diagnosis of multilocular cyst, they ignored the suggested modifications of Boggs and Kimmelstiel (1956), which would have allowed classification of several of the cases as multilocular cysts. This paper, whilst adding to the confusion in this area, did restate the valuable observations that all of the described cases which included embryonal or nephroblastomatous elements occurred in children less than 2 years of age and that in all cases where follow-up information was available, there were no reports of recurrence or metastasis, (disease free intervals ranging from 5–63 months). This observation was tempered with the speculative warning that lesions containing varying proportions of undifferentiated and partially differentiated metanephric tissues might have the potential for more aggressive behaviour. The authors felt it reasonable, however, to perform nephrectomy alone as primary therapy for such cases except in the case of inadequate resection, in which situation they felt that additional therapy was indicated.

Conclusions

The case reported in this paper fulfills the criteria indicated for the diagnosis of multilocular renal cyst. The ultrastructural appearances of this lesion, described for the first time, confirm the epithelial nature of the cyst lining, which has the general configuration of simplified renal tubular epithelium. The presence of extensive calcification and bone formation is an unusual feature. The possibility that this might represent persisting heterologous, fully differentiated nephroblastomatous tissues might be considered but the development of this component by dystrophic and metaplastic processes seems equally likely.

There is now an increasing body of literature describing lesions, always in infants, macroscopically identical to multilocular renal cyst, which contain variably differentiated nephroblastomatous foci. Such cases have generated terminologic confusion but raise the intriguing possibility that at least some, if not all, multilocular cysts are the product of differentiation and maturation of Wilms' tumours and may represent one end of a spectrum, the intermediate components of which are represented by either Wilms' tumours showing varying cystic change and degrees of differentiation, or by multilocular cysts containing nephroblastomatous foci. This plausible hypothesis remains unproven. The presentation of multilocular cysts in old age and in kidneys apparently normal on previous urographic examination would require the presupposition that the precursor lesions must have remained very small for many years, becoming detectable only as cystic dilatation of preformed tubular structures occurred. The usual absence of differentiated heterologous elements (such as striated muscle) in multilocular cysts would also be difficult to explain. The statement by Dainko et al. (1963) that cartilage is "occasionally" found is unsubstantiated; however, Kissane (1974) stated that "dysontogenetic tissue,.....rarely including striated muscle, cartilage or bone" may be seen in the "capsule external to the lining".

This review of reports of those cases ostensibly showing evidence of a nephroblastomatous component shows that several cases have been so designated solely on the basis of the presence of septal tubules. In future studies of these lesions, the group containing unequivocal nephroblastomatous elements should not be catalogued together with such ambiguous cases. The tubular structures described may be the result of differentiation of nephroblastomatous elements, but there is no evidence that they are and the possibility remains that they represent sequestration or disordered development of normal tubules. The author is not in agreement with the implication of Joshi et al. (1977) that the differences between "cystic partially differentiated nephroblastoma" and multilocular cysts are distinct, because this approach fails to recognise the pathogenetic dilemma outlined above.

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