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A case of renal angiomyolipomas associated with multiple and various hamartomatous microlesions

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Summary. A case of 50-year-old woman who demonstrated large intrarenal and externally protruding angiomyolipomas (AMLomas), unusual intraglomerular lesions and multiple hamartomatous microlesions of various types within the kidney is reported. This type of intraglomerular lesion has been briefly described only twice previously in patients with tuberous sclerosis (TS), and is unique in its location and histological appearance. The lesions are mainly composed of proliferating mesangial cells and are hamartomatous in nature. Although no stigmata of TS other than renal AMLomas are apparent in this case, the presence of many renal hamartomatous lesions suggests the possibility of a forme fruste of TS.

Key words: Intraglomerular lesions – Renal angiomyolipoma (AMLoma) – Tuberous sclerosis (TS) – Forme fruste of TS

Introduction

Renal angiomyolipoma (AMLoma) is one of the characteristic lesions occurring in tuberous sclerosis (TS) (Arai et al. 1979; Hiraishi et al. 1974; Takashi et al. 1984; Taylor and Genters 1958), but it is also observed in patients without evidence of TS. It is also known that AMLoma, with or without TS, is often associated with various other renal lesions (Hiraishi et al. 1974), such as cysts (Reed et al. 1963; Wentzl et al. 1970; Rosenberg et al. 1975; Michel et al. 1983), hamartomas (Moolten et al. 1942; Chonko et al. 1974) and renal cell carcinomas (Takashi et al. 1984).

This paper presents a case of renal AMLomas associated with peculiar intraglomerular hamartomatous lesions, which have rarely been described, in addition to various types of multiple, small renal hamartomata. The nature and significance of these intraglomerular lesions are discussed.

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Materials and methods

The patient was a 50-year-old Japanese housewife who was found to have asymptomatic haematuria during a routine health check-up. Physical examination on admission was normal, but cystoscopic examination revealed passage of bloody urine from the right ureteric orifice. Computerized tomography showed two space-occupying lesions in the right kidney, one at the surface, and the other in the medulla. The left kidney showed no remarkable abnormalities. Laboratory studies were not contributory.

With a diagnosis of multiple tumours of the right kidney, resection of the right kidney and adrenal gland was performed, along with regional lymph nodes dissection, on October 21, 1985. Postoperatively, the patient has been doing well without chemotherapy.

The family history was carefully examined but no member showed evidence of TS (mental, dermatological or genitourinary manifestations).

Pathology. The resected right kidney measured $10 \times 5.5 \times 4.4$ cm and weighed 130 g. There was no adhesion to the perirenal adipose tissue. A dark-red fungiform tumour measuring $3.5 \times 3.5 \times 1.5$ cm protruded from the anterior surface of the middle portion and was grossly demarcated from the renal parenchyma. The outer surface of the tumour was covered with fibrous tissue which was continuous with the renal capsule.

Cut sections revealed another tumour in the medulla, which was well-demarcated, yellowish and measured 2×1.8 cm. In addition to these two large tumours, there were multiple small slightly elevated subcapsular lesions and several cortical round withish nodules, measuring up to 5 mm in diameter. The regional lymph nodes and the adrenal gland were unremarkable.

Histologically, the two large tumours showed basically similar findings typical of the classical renal angiomyolipoma (AMLomas) being composed of mature adipose tissue mixed with spindle-shaped myogenic cells and thick-walled blood vessels in various proportions. Mitotic figures, cellular atypism and giant cell formation were not observed in these tumours.

The subcapsular nodules were chiefly composed of spindle-shaped cells which showed fascicular and interlacing arrange-

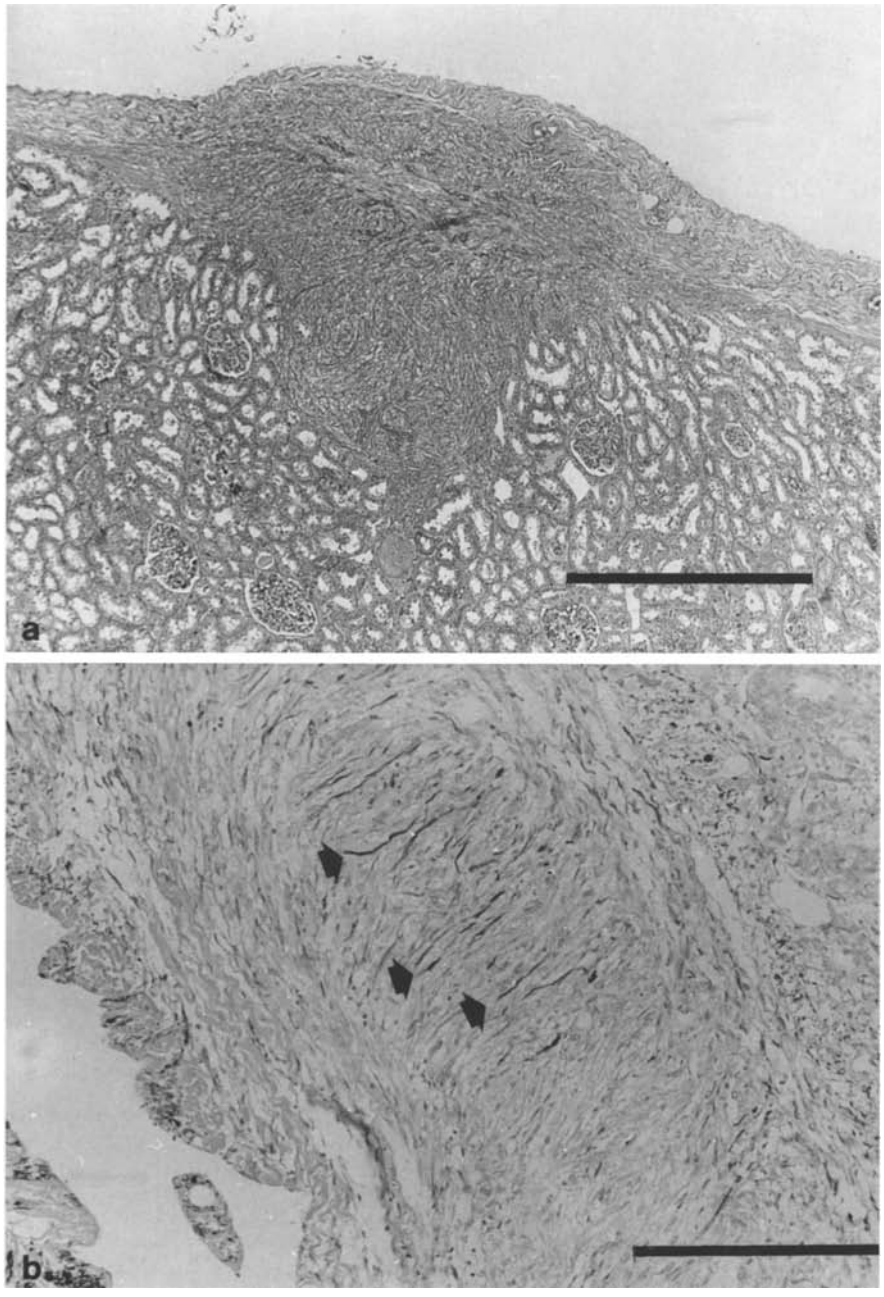

Fig. 1. Histology of the subcapsular nodules. This type of tumours was formed by fascicularily-arranged spindle cells (**1a**; H & E, ×16.7, Bar; 500 μm), which were desmin-positive (**1b** *arrows*, Anti-desmin polyclonal antibody, PAP method, ×83.3, Bar; 100 μm)

ments with oval-shaped nuclei (Fig. 1a). The fibrous stroma was relatively rich and no defifite demarcation between the renal cortical structures was seen. Normal-appearing tubular structures were frequently observed in these lesions, but they were thought to be entrapped preexisting renal tissue.

The small cortical nodules were composed of large clear cells with vesicular nuclei (Fig. 2). Some of these cells were arranged in glandular patterns with mucinous material in the central luminal spaces. The nuclei of these cells showed slight or moderate atypia. The stroma was very scanty and showed rich sinusoid-like capillaries surrounding the tumour cells.

In addition to these hamartomatous lesions, considerable numbers of the glomerular corpuscles showed peculiar intraglomerular lesions attached to the glomerular tufts (Fig. 3a). They were composed of compactly arranged round to polygonal-shaped cuboidal cells, with relatively small nuclei and abundant cytoplasm. The nuclei were round, but occasional cleaved forms were noted. No cellular atypia or mitotic figures were apparent. Within these lesions, scattered vacuolar spaces surrounded by the above-mentioned cuboidal cells were present. Oil red-O staining revealed fat droplets in these lesions (Fig. 3b). PAS and PAM stainings revealed that they were bound by basement membranes which were continuous with the basement membrane of the glomerular loops (Fig. 3c). With PAS staining, the cuboidal cells of the intraglomerular lesions had weak and nongranular positivity in the perinuclear cytoplasm, which was not digested by diastase treatment. Collagen fibers were detected in the intraglomerular lesions by Masson's trichrome staining.

Within the medullary ray, a circumscribed small lesion was

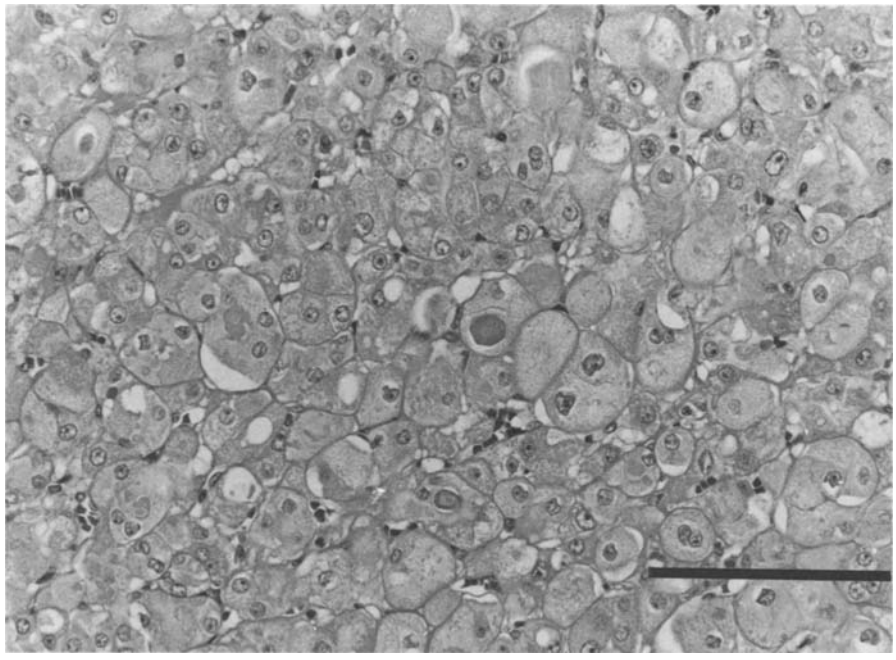

Fig. 2. Cortical nodular lesions composed of large vacuolar cells arranged in tubular manner, suggesting an epithelial nature. Mitotic figure and cellular atypia are slight. PAS-positive material was found in luminal areas. (H & E, ×417, Bar; 20 μm)

found, which was composed of aggregations of the dilated tubuli with fibrous stromal reaction. The epithelium of the tubuli was simple cuboidal or columnar form and the cells were somewhat larger than normal collecting duct epithelial cells, but no atypia was observed.

Immunohistochemistry. Formalin-fixed and paraffin-embedded tissues were cut and treated with hydrogen peroxide to block endogenous peroxidase activity after deparaffinization.

The sections were reacted with primary antibodies for 1 h at 37 Ca, washed with phosphate-buffered saline (PBS) followed by peroxidase-anti-peroxidase (PAP) or by the indirect method, and reacted with DAB for demonstration of the localization of the antigens.

Primary antibodies used in this study included rabbit anti-S-100 protein polyclonal (DAKO, diluted 1:100), rabbit anti-desmin polyclonal (Bio-Science, diluted 1:100), rabbit anti-factor VIII-related antigen monoclonal (DAKO, diluted 1:100), mouse anti-vimentin monoclonal (DAKO, diluted 1:100), rabbit anti-epidermal cytokeratin polyclonal (DAKO, diluted 1:100) antibodies.

Immunohistochemical study of the AMLomas showed that S-100 protein was positive in adipose cells, and that factor VIII-related antigen was positive in the endothelial cells of tumour blood vessels.

The spindle-shaped cells of the subcapsular nodules were desmin-positive, but negative for the other markers (Fig. 1b).

Clear cells of the cortical nodular lesions and epithelial cells of nodular dysgenesis in the medulla were positive for S-100 protein and keratin, but negative for the other markers.

The cuboidal cells of the intraglomerular lesions failed to show any demonstrably positive reaction to the markers examined. However, S-100 protein was demonstrated in the fat cells, and factor VIII-related antigen was shown in the vascular cells within the intraglomerular lesions. Vimentin was detected in the cells forming the outermost cell layers surrounding the intraglomerular lesions and basement membrane (Fig. 3d).

Discussion

The unique features in this case were the presence of many small subcapsular and cortical nodules and peculiar intraglomerular lesions, in addition to the large AMLomas showing classical histological features. The intraglomerular nodular lesions merit particular attention. Intraglomerular lesions in patients of TS have been previously described only in two papers. Feriz (1930) first reported such changes and described low-cuboidal-shaped cells surrounding fat-positive vacuoles in the intraglomerular lesions. He named them "epithelial" or "fatty inclusions" in the glomerular loops. However, we consider that the former is not an appropriate term; the cells lack apparent epithelial characteristics and the space mimicking the glandular lumen contained fat droplets. In Japan, Shinohara et al. (1973) described this type of glomerular change associated with TS, but they did not comment on the nature of the lesion in detail.

Our study revealed that the intraglomerular lesions had basement membranes which were continuous with the basement membrane of the glomerular tufts, and covered with vimentin-positive podocytes. Some of the intraglomerular lesions also contained adipose tissue, which was proved by oil red-O and S-100 protein staining. On the basis of topographic relationships of the above-mentioned cellular elements, we consider that these proliferating cuboidal cells in the intraglomerular lesions

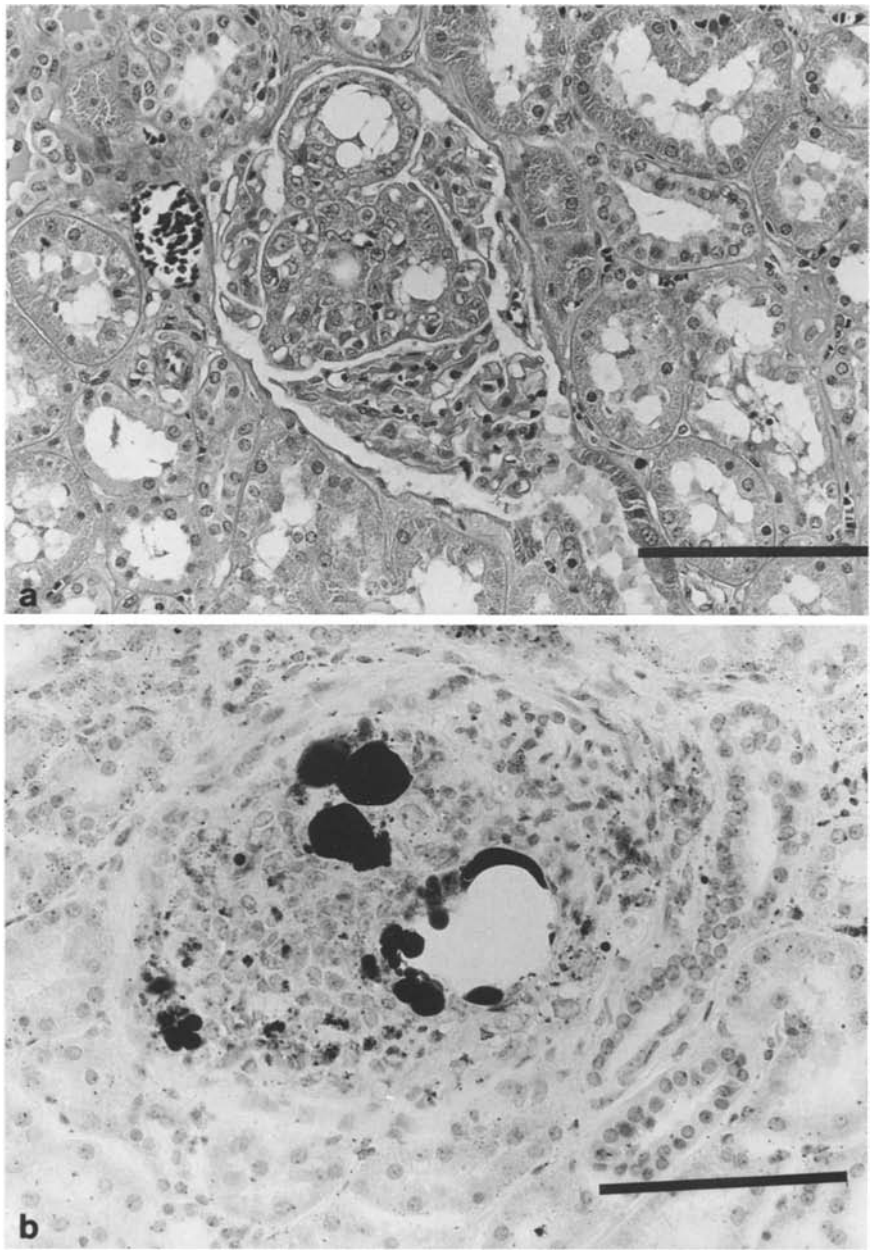

Fig. 3. Intraglomerular lesions. (**a**) In the glomerulus, abnormal cell clusters containing vacuole and a partial pseudoepithelial arrangement should be noted. The normal glomerular loop was compressed, but not destroyed. (H & E, ×83.3, Bar; 100 μm). (**b**) Lipid droplets were positively stained by oil red-O method, within the intraglomerular lesion and indicate the hamartomatous nature of these lesions. (Oil red-O, ×83.3, Bar; 100 μm)

were probably related to the mesangial cells, although no supportive evidence by immunohistochemical studies were obtained.

As to the subcapsular nodules, the major element of the nodules was myogenic and they had hamartomatous features. This type of lesion was previously described as a "capsuloma" (Colvin 1942). It is also considered that these nodules have some relationship to renal AMLomas, because "capsulomas" tend to be multiple when AMLoma associated.

The cortical nodules have been well described in TS. Risdon (1981) noted that cortical hamartoma of the kidney associated with AMLoma in patients with TS is not uncommon and that these lesions frequently break down to form pseudocysts in the kidney. However, in our case, cystic changes were not observed. A small cystic lesion in the medullary ray noted in this case was histologically identical with so-called nodular dysgenesis as described by Miranda (1971) designated collecting tubule hamartoma by Finegold (1970).

As mentioned above the different types of microlesion found in the present case are known to be associated with TS as well as AMLoma and are thought to be hamartomatous in nature. TS

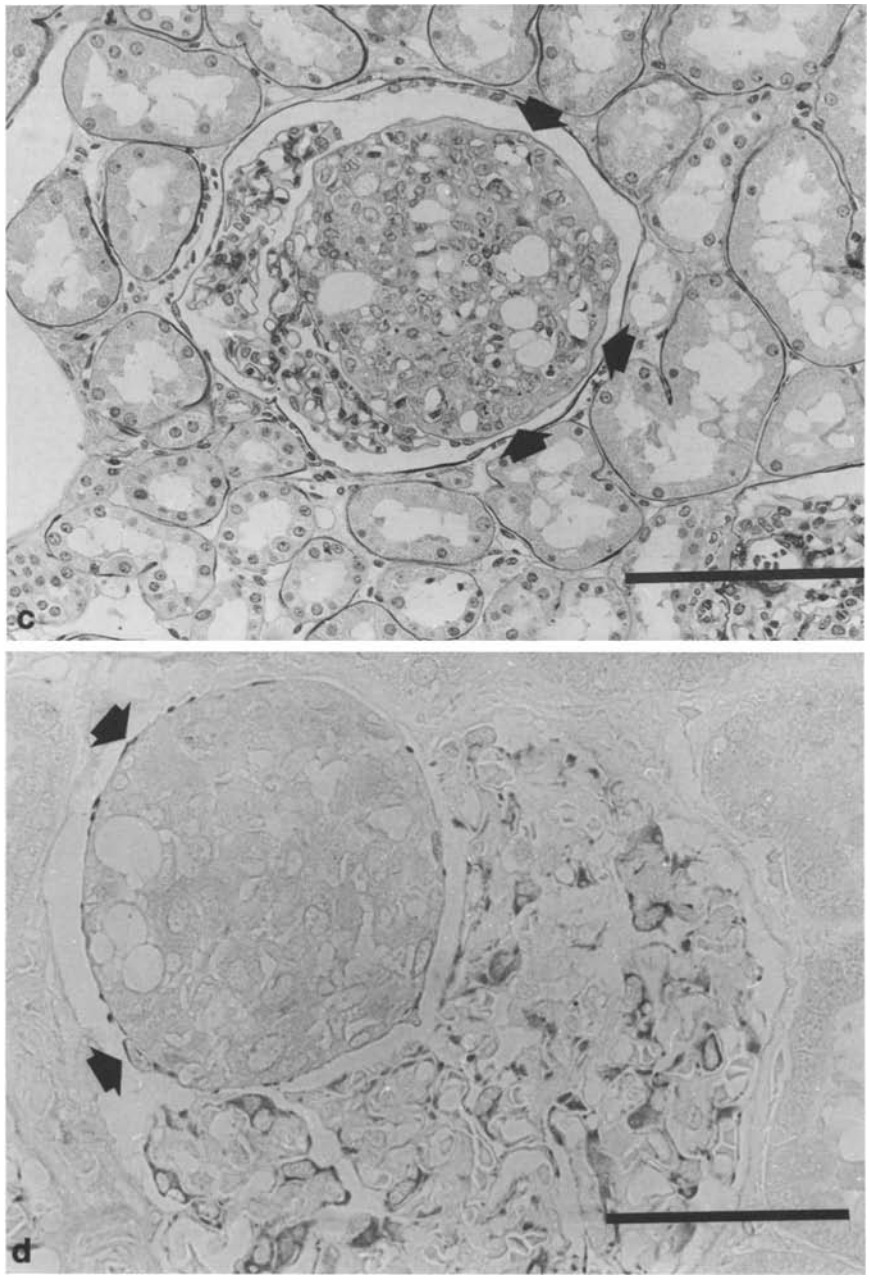

Fig. 3c. PAM stain revealed that basement membrane is continuous with the normal glomerular loop surrounding the intraglomerular lesion (*arrows*). This finding suggested that this lesion was protruding from glomerular loop within the same Bowmann's corpuscle. (PAM, ×83.3, Bar; 100 μm). (**d**) Anti-vimentin antibody reacted with outermost cell layer composed of epithelial cells covering the basement membrane of the intraglomerular lesion and normal glomerular loop (*arrows*). (Anti-vimentin monoclonal antibody, Indirect method, ×167, Bar; 50 μm)

is a hereditary condition in which multifocal and hamartomatous lesions develop in various organs. Clinically, seizures, mental retardation, brain tumours, renal hamartomas (including AMLoma), adenoma sebaceum of the face and leukoplakia of the skin are well known manifestations. Among these features, renal AMLomas are well known and have been fully described in previous papers. Eighty percent of cases of TS are associated with renal AMLomas, while 50% of patients with AMLoma have other stigmata of TS. On the basis of such an intimate relationship between these two conditions, Chonko et al. (1974) considered patients with AMLoma but without other stigmata of TS as formes fruste of TS.

The present patient did not show any signs of TS other than AMLomas, but the presence of the hamartomatous renal lesions strongly suggested that this case was a forme fruste of TS. Careful examination of the entire kidney is required in AMLomas, as the organ may contain hamartomatous lesions indicative of a forme fruste of TS.

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References

Arai Y, Pak K, Okabe T, Komatsu Y, Yoshida O (1979) Bilateral renal angiomyolipoma with no other tuberous sclerosis complex. Acta Urol Jpn (in Japanese) 25:805–811

Chonko AM, Weiss SM, Stein JH, Ferris TS (1974) Renal involvement of tuberous sclerosis. Am J Med 56:124–132

Colvin S (1942) Certain capsular or subcapsular mixed tumor of the kidney, herein called "capsuloma". J Urol 48:585–600

Feriz H (1930) Ein Beitrag zur Histopathologie der tuberculosen Sclerose. Virchows Arch A (Pathol Anat) 278:690–769

Finegold MJ (1970) Collecting tubule hamartoma: Another form of renal dysplasia. Arch Pathol 90:31–34

Hiraishi K, Tsumagari I, Tao S (1974) A case of Bourneville-Pringle phacomatosis, a case report and statistical consideration. Clin Urol (in Japanese) 28:41–47

Michel JM, Diggle JH, Brice J, Mellor DH, Small P (1983) Two half-sibring with tuberous sclerosis, polycystic kidneys and hypertension. Developing Med Child Nephrol 25:239–244

Miranda D, Schinella RA, Finegold MJ (1971) Nodular dysgenesis of renal tubules. An early stage in pathogenesis of polycystic kidneys. Arch Pathol 92:377–383

Moolten SE (1942) Hamartial nature of the tuberous sclerosis complex and its bearing on the tumor problems. Arch Int Med 69:589–602

Reed WB, Calif R, Nickel WR, Campion G (1975) Internal manifestations of tuberous sclerosis. Arch Dermatol 87:715–728

Risdon RA (1981) Diseases of the kidney and lower urinary tract. In: Berry CL (eds) Paediatric Pathology. Springer, Berlin Heidelberg New York Tokyo, pp 438

Rosenberg JC, Bernstein J, Rosenberg B (1975) Renal cystic disease associated with tuberous sclerosis complex. Renal failure treated by cadaveric kidney transplantation. Clin Nephrol 4:109–112

Shinohara S, Kosugi Y, Fujitani K, Higami S, Miki T, Kobayashi Y (1973) Clinical aspects of tuberous sclerosis. Early symptoms and electroencephagram of patients and their relatives. Brain and Nerve (in Japanese) 25:1317–1334

Takashi M, Murase T, Yamamoto M, Sobajima T, Miyake K, Mitsuya H, Soma T, Ogisu B, Watanabe J, Ootake H (1984) Three cases of renal angiomyolipomas. Statistics of 194 cases of angiomyolipomas reported in Japan. Acta Urol Jpn (in Japanese) 30:65–75

Taylor JN and Genters K (1958) Renal angiomyolipoma and tuberous sclerosis. J Urol 79:685–696

Wenzl JE, Lagos JC, Albers DD (1970) Tuberous sclerosis presenting as polycystic kidneys and seizures in an infant. J Pedia 77:673–676

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