

Cystic angiomyolipoma of the kidney: a clinicopathologic description of 11 cases

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This report deals with 11 examples of renal angiomyolipomas (AML) which appear to include an epithelial element as a part of the neoplasm in the form of gross or microscopic cysts—usually both. There were seven females and four males between the ages of 20 and 70 years with mean age of 45 years. Three of these were known to be symptomatic: intermittent flank pain and gross hematuria for 2 months; recurrent hematuria both before and after flank trauma and a third patient with acute abdomen due to a ruptured tumor blood vessel. Cysts were described in three of the six cases where radiographic data were available. Seven tumors were in the right kidney and four in the left. In gross descriptions, cysts were mentioned in seven and they ranged from 6.0 to 2.0 cm with a median and mean maximal diameter of 5.0 and 4.0 cm, respectively. Microscopically, virtually all of the tumors included multiple smaller cysts and these were lined by flat, cuboidal or columnar epithelium and occasionally hobnail epithelium. There was usually a subepithelial collar of poorly differentiated cells, but the solid element of all tumors was myomatous angiomyolipoma; only one case had any adipose tissue. A dominant histological feature was the prominent lymphatic channels—identical to those of lymphangiomyomas and myomatous or triphasic AMLs. They are much more conspicuous in these cystic cases. Immunohistochemically, all tumors tested were reactive with actin, desmin and HMB-45, with the latter being more intensely positive in the subepithelial collars. Estrogen and progesterone receptors were usually positive, also. The behavior of these lesions appears to be no different from that of other AMLs.

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Over the years it has been our impression that no benign tumor of the genitourinary system was more often misinterpreted as malignant than the renal angiomyolipoma (AML). The great majority are of course the typical triphasic lesions with smooth muscle, adipose tissue and the characteristic blood vessels but it is very common for the muscle cells to show nuclear variations and/or epithelioid features which cause concern. Those which show very few or no fat cells are frequently regarded as sarcomas or sarcomatoid carcinomas and those with very few muscle cells are often interpreted as liposarcoma—particularly those that arise from the renal capsule and expand entirely into the perinephric soft tissue. Over the past 34 years (1970–2004) we have seen 1064 renal AMLs at the AFIP and only 11 of them show the features to be described here. Although

these were not often regarded as malignant only two were recognized as AML (Table 1).

Materials and methods

Hematoxylin and eosin (H&E)-stained slides were available on all cases and unstained slides and/or blocks from formalin-fixed, paraffin-embedded tissue were available for 10 of the 11 cases. Copies of original pathology reports were available on all cases and radiology reports on six. Follow-up was available in five cases. In addition to H&E stains, immunohistochemical studies were performed on 10 cases (Tables 2 and 3).

Results

Clinical Features

Patients ages ranged from 20 to 70 years with median and mean age both of 45 years. Females predominated 7:4 and the right kidney predominated 7:4. Three patients are known to have had symptoms related to the tumor. In case 2 there had

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Table 1 Original pathologic diagnosis

Case 1	Hemorrhagic renal cyst
Case 2	Hemangiopericytoma
Case 3	Nephroblastoma (variant of AML)
Case 4	No diagnosis
Case 5	Ruptured aneurysm due to fibromuscular dysplasia
Case 6	Hamartoma
Cases 7 and 8	Mixed epithelial–stromal tumor
Cases 9 and 10	AML with entrapped renal tubules
Case 11	Benign multilocular cyst

been intermitted flank pain and gross hematuria for 2 months. In case 5 the patient had an acute abdomen due to rupture of an AML blood vessel and in case 6 there had been recurrent hematuria for several months both before and after an episode of flank trauma. In three cases the renal tumors were discovered incidentally and in five cases no comment had been made regarding clinical presentation. In six cases we had received information about radiographic findings and cysts were described in three of them. Follow-up information was available on five cases: cases 1, 2, 3 and 7 were without evident disease at 3 years, 9 years, 3 years and 6 months, respectively. Case 4 died of unrelated disease at 3 years. Based upon available clinical information, none of the 11 patients had evidence of tuberous sclerosis or lymphangio-myomatosis. It is not known if any of them had taken estrogen.

Gross Pathology

Cysts were mentioned in seven of the gross descriptions (Figures 1 and 2). They measured from 6.0 to 2.0 cm in maximum diameter with a median of 5.0 cm and a mean of 4.0 cm. Not described as grossly cystic were case 2 which had multiple collapsed cysts microscopically, case 4 (partially cystic) had five or six cysts of indeterminate size, case 5 with the extensive hemorrhage had a microscopic cyst near the ruptured vessel (Figure 3) which extended through the adjacent renal medulla and in case 10, two cysts approximated 1.0 and 0.5 cm microscopically.

Microscopic Pathology

Most of the cases had multiple smaller cysts, usually about 0.5 cm and less all lined by eosinophilic cells which varied from flat to cuboidal, columnar and/or hobnail. In most cases, but not all, there was a subepithelial layer of small, undifferentiated cells, forming a ‘cambium-like’ layer and peripheral to this the solid element of the tumors consisted of what we will describe here as ‘myomatous angiomyolipoma’—meaning that a lipomatous component was not present (Figures 4–6). The one

Table 2 Antibodies used for immunohistochemistry

Antibody	Dilution	Pretreatment	Vendor
HMB45	1:80	None	Enzo (Diagnostic, Farmingdale, NY, USA)
SM Actin	1:160	Micro	Dako (Carpinteria, CA, USA)
Desmin	1:160	Micro	Dako (Carpinteria, CA, USA)
ER	1:30	Micro	Novocastra (Newcastle-upon-Tyne, UK)
PR	1:160	Micro	Novocastra (Newcastle-upon-Tyne, UK)
Melan A	1:40	Micro	Novocastra (Newcastle-upon-Tyne, UK)
		Tyrosinase	1:160
Micro		Novocastra (Newcastle-upon-Tyne, UK)	
MITF	1:80	Micro	LabVision (Fremont, CA, USA)
Keratin	1:1280	Protease	Boehringer (Indianapolis, IN, USA)
D2-40	1:20	None	Biocare Medical (Walnut Creek, CA, USA)

exception was case 10 where the solid tumor was about 20% adipose. Cases 3 and 9 had typical AMLs in remote parts of the kidney (Figure 2). In case 1 the nodular cystic contour (Figure 1) and in case 9 the cystic septations described radiographically, were due to smooth muscle forming septa between cysts (Figures 2 and 7). It was usually possible to demonstrate the thick-walled or cellular vessels characteristic of typical AMLs (Figures 8 and 9) but, in addition to the usual absence of fat cells, a dominant feature in all cases was the prominent branching and curvilinear spaces identical to those seen in lymphangio-myomatosis (Figures 10–12). These can usually be seen in the myomatous element of AMLs but they were much more numerous in these cystic lesions.

Incidental findings included multiple papillary adenomas in the adjacent renal cortex in case 7 and, in case 1, a 1.0 cm papillary renal cell carcinoma, type 1, grade 1 was within the wall of the cyst.

Immunohistochemical Findings

Immunohistochemistry was performed on 10 of 11 cases with the following results (positive/negative cases): smooth muscle actin 10/0, desmin 8/0, keratin (cysts) 7/0, HMB-45 10/0, Melan A 2/0, tyrosinase 1/0, MITF 1/0, estrogen receptor 7/2 and progesterone receptor 8/1.

In the other case (case 9), the contributing pathologist found positive SMA, HMB-45 and estrogen and progesterone receptors. It was interesting to note that the HMB-45 reaction was usually

Table 3 Clinicopathologic features of the study group

	Age (years)	Sex	Side	Clinical presentation	Imaging	Treatment	Gross pathology
Case 1	61	F	L	Incidental finding	Retrograde pyelogram: large cyst distorting pelvocalyceal system. Brown's fluid aspirated	Nephrectomy	6.0 cm upper pole cyst with focal nodular luminal contour
Case 2	45	F	R	Intermittent flank pain and gross hematuria for 2 months	Excretory urogram: Right lower pole mass	Nephrectomy	Circumscribed 3.5 cm yellow-gray tumor
Case 3	21	F	R	NA	NA	Nephrectomy	5.0 cm cyst in upper pole. Lower pole: tan, hemorrhagic $7 \times 4 \times 3 \text{ cm}^3$ mass
Case 4	37	F	R	Incidental finding in diabetic nephropathy	Vascular lower pole tumor by angiography	Partial nephrectomy	A 'partially cystic' gray-white tumor $5 \times 4 \times 3 \text{ cm}^3$
Case 5	39	F	L	Retroperitoneal hemorrhage with acute abdomen from ruptured vessel in hilus	NA	Nephrectomy	Tumor obscured by extensive hemorrhage at renal hilus
Case 6	20	M	L	Recurrent hematuria several months before and after flank trauma	Mass in the lower pole	Partial nephrectomy	A 5.0 cm cyst filled with blood clot
Case 7	70	M	R	NA	NA	Partial nephrectomy	A 2.0 cm cyst with folding of luminal contour. $4 \times 3 \text{ cm}^2$ nodule in wall of cyst
Case 8	27	F	R	NA	CT scan: 2.5 cm, largely exophytic cyst with some peripheral enhancement	Nephrectomy	A $3 \times 2.7 \times 2 \text{ cm}^3$ cystic mass protrudes from renal surface. Cut surface: multicystic
Case 9	61	F	R	Incidental finding on metastatic survey for lung cancer	Ultrasound: complex exophytic cyst laterally, with septations. $3.8 \times 3 \times 2.6 \text{ cm}^3$ solid mass in lower pole	Nephrectomy	Hemorrhagic capsular cyst $5 \times 4 \times 2.5 \text{ cm}^3$ laterally. Lower pole: $3.5 \times 3.1 \times 2.5 \text{ cm}^3$ mass
Case 10	50	M	R	NA	NA	Partial nephrectomy	White-tan nodule. Size not given
Case 11	67	M	L	NA	NA	Excision	Exophytic mass $3 \times 2.7 \times 1.8 \text{ cm}^3$ with a 2.7 cm cyst with clear fluid

NA: not available.



Figure 1 Case 1 had a nodular luminal contour (due to small cysts and smooth muscle).

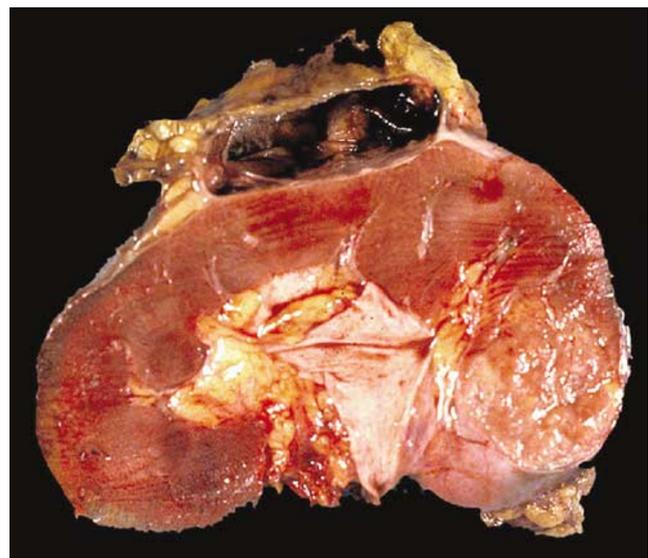


Figure 2 Case 9: triphasic AML at right and hemorrhagic cystic AML.

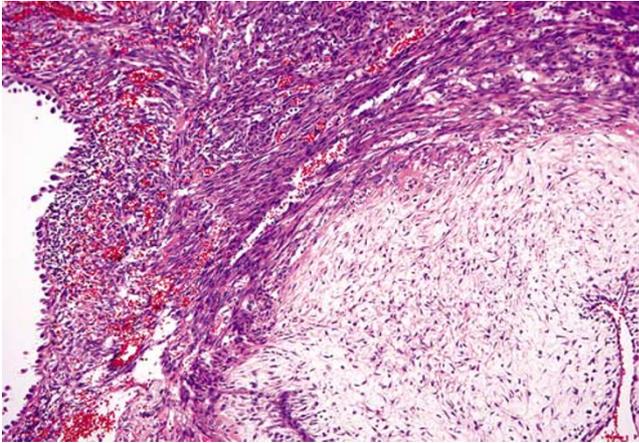


Figure 3 Case 5: the AML vessel that ruptured and the epithelial-lined cyst at left. H&E $\times 80$.

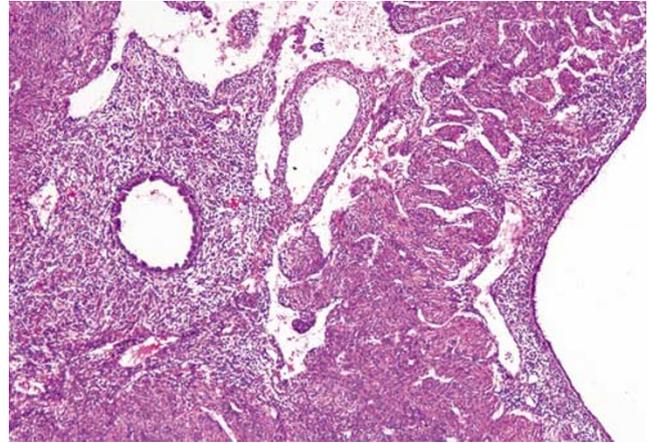


Figure 6 The composite features of cystic AML: large and small cysts with prominent lymphatics and collars of smaller cells. H&E $\times 48$.

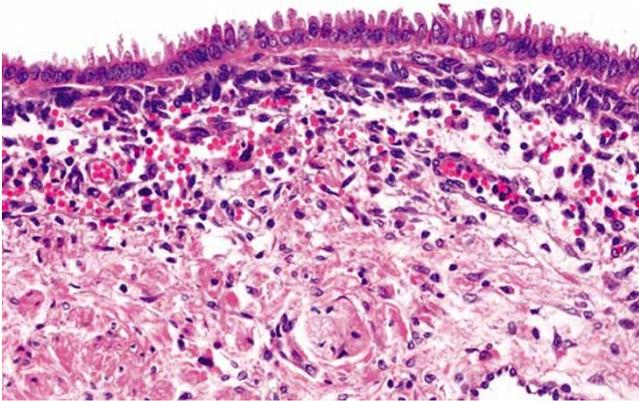


Figure 4 Columnar epithelial lining with 'cambium-like' layer of cells. H&E $\times 223$.

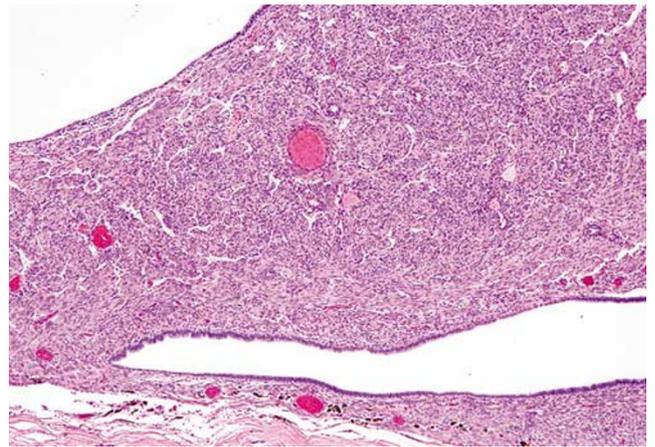


Figure 7 Case 9: the septations seen on ultrasound were formed by myomatous AML. H&E $\times 48$.

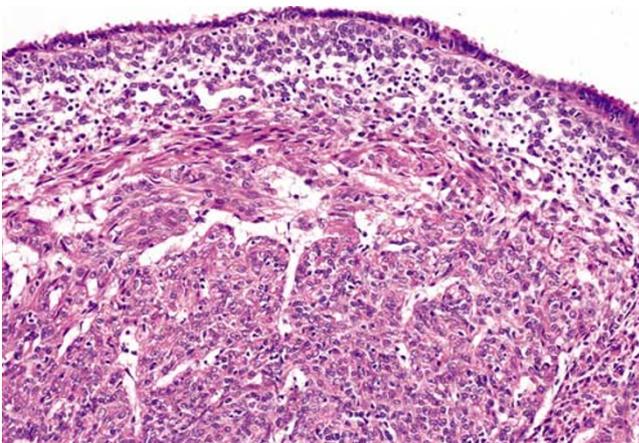


Figure 5 The common appearance of cystic AML. Note prominent lymphatic spaces. H&E $\times 150$.

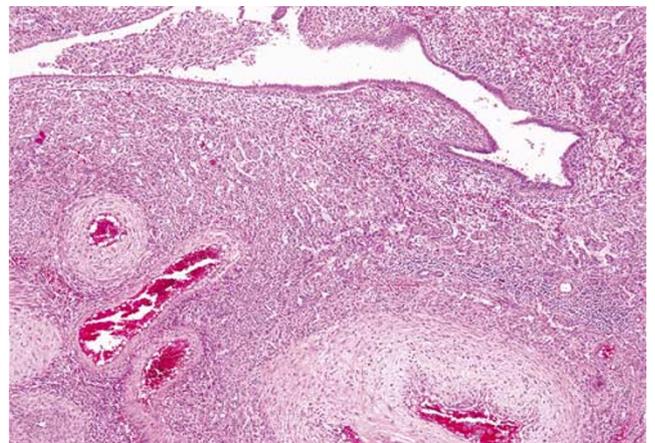


Figure 8 Note AML-type vessels with lymphatic-rich smooth muscle and cyst at top. H&E $\times 48$.

much more intense in the subepithelial 'cambium-like' zone (Figure 13), and this was often true, also, for the estrogen and progesterone receptors (Figure 14).

Discussion

Two of the more recent cases were sent to us as mixed epithelial–stromal tumors and this will likely

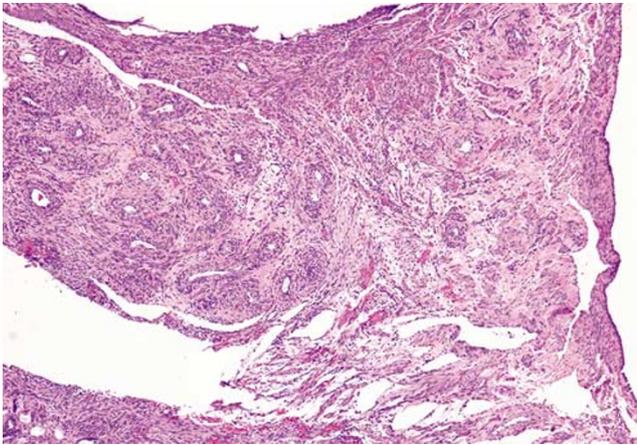


Figure 9 Case 11 was entirely exophytic. Renal capsule (lower left) is smooth muscle. Cysts at top and right with AML vessels. H&E $\times 48$.

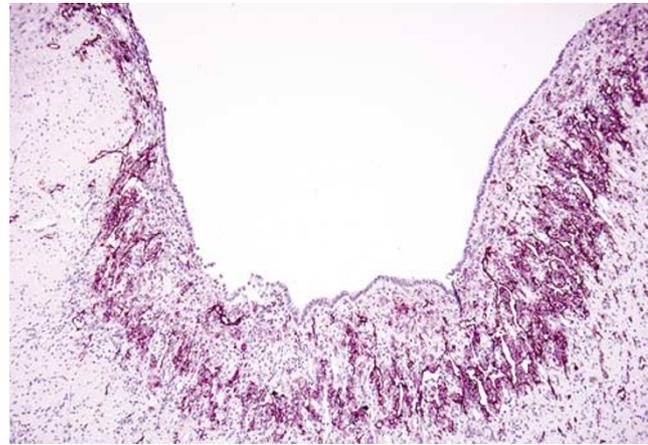


Figure 12 Prominent lymphatics in myomatous AML collar beneath the epithelium. D2-40 $\times 80$.

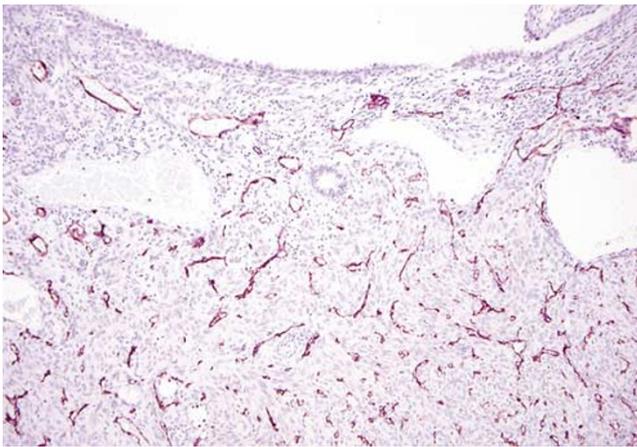


Figure 10 Note prominent lymphatic channels in the smooth muscle. D2-40 $\times 80$.

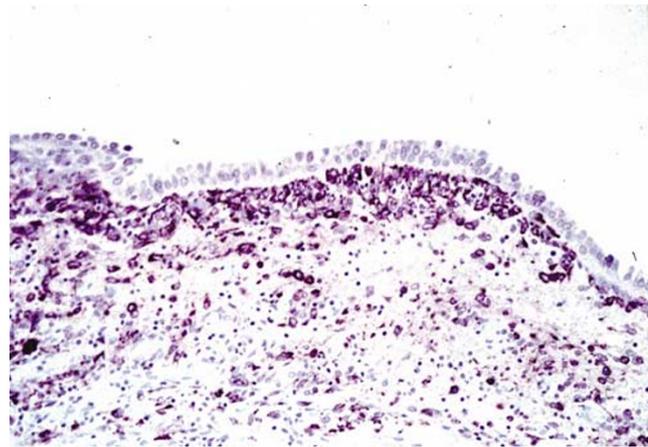


Figure 13 The HMB-45 reaction is usually more intense in the subepithelial cells. $\times 160$

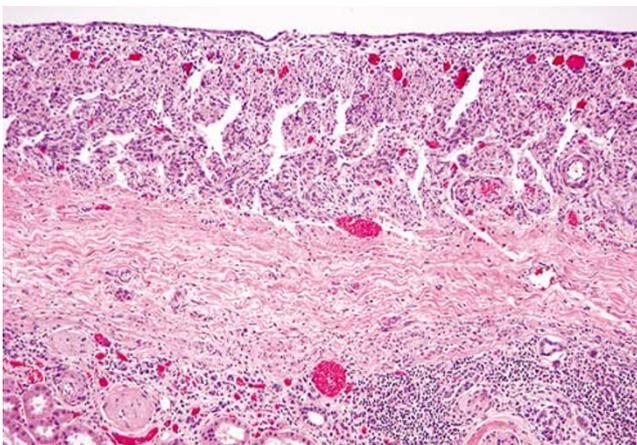


Figure 11 Case 9 was extracapsular. Note renal capsule (center field) and prominent lymphatics in band of subepithelial tumor. H&E $\times 80$.

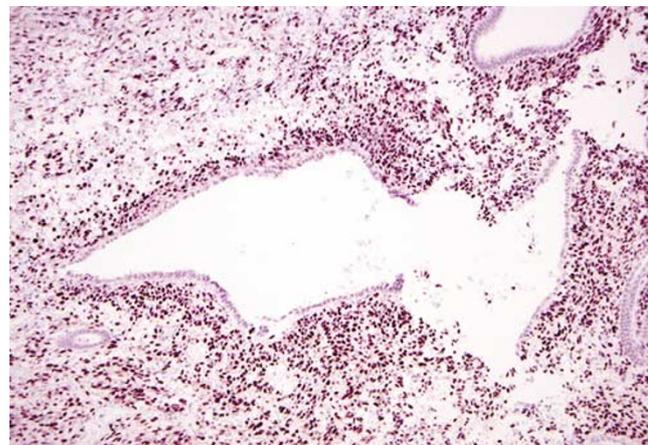


Figure 14 Case 8: progesterone and estrogen receptors are often more reactive in the subepithelial cells. Progesterone receptor $\times 80$.

continue to be the chief differential diagnostic consideration.^{1,2} These are the tumors that previously were classified as cystic hamartomas of the

renal pelvis,³⁻⁵ adult mesoblastic nephroma⁶ or renal pelvic or cortical hamartomas.⁷ Like the cystic AMLs they occur usually in adult females with

mean ages in the forties. Like the cystic AMLs they may have gross and microscopic cysts and they usually have variable quantities of smooth muscle—either in sheets or discrete fascicles. The epithelium consists of tubular or tubulopapillary elements, often aggregated in an adenoma-like morphology with occasional epithelial-lined fibrous nodules. Expanses of stroma may be cellular or acellular fibrous tissue and sheets or collars of a primitive, ‘Mullerian-like’ stromal element. Fat cells may also be present. These are negative for the melanoma markers.

In contrast, the cystic AMLs usually will show the characteristic vessels and, as described above, the slit-like branching and curvilinear spaces are a prominent and constant feature, identical to those seen in lymphangiomyomas and, focally, in most triphasic or myomatous AMLs.^{8,9} For this study we have illustrated the recently described monoclonal antibody D2-40 which specifically recognizes human podoplanin and reacts with lymphatic but not blood vascular endothelial cells.¹⁰ We have not noted these prominent lymphatic features in other spindle cell tumors of the kidney, but with this new methodology this will likely be specifically addressed in future studies. Lastly, tuberous sclerosis may have renal cysts, but we did not find epithelium with the large voluminous amounts of cytoplasm in the cysts of these 11 cases.¹¹

There remains the question of whether these cysts represent entrapped renal tubular elements. We believe they do not. Two of these cases were interpreted as such and Leung *et al*¹² have described AMLs with entrapped tubular elements showing variable cystic dilatation, but we have not seen anything illustrated which resembles the 11 cases described here. As described by Eble⁸ we often see entrapped renal tubules in the extreme periphery of AMLs but these do not usually have a particularly cystic appearance. In none of these did the cysts appear to be concentrated in the periphery of the solid tumor. We are not aware of any immunohistochemical study that would distinguish entrapped renal tubules specifically, so this was not attempted. Most persuasive were those cystic AMLs that were entirely external to the kidney with prominent cysts where one would not expect to see entrapped parenchyma. The behavior of these tumors appears to be no different from other AMLs. One of the 11 patients had massive hemorrhage and several of them had hemorrhage in the cyst wall or lumen.

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Declaration

The opinions and assertions contained herein are the views of the authors and do not reflect the official views of the Department of the Army or the Department of Defense.

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