

Case Report

Cysts in angiomyolipoma with epithelial cysts may be consisted of entrapped and dilated renal tubules: report of a case with additional immunohistochemical evidence to the pre-existing literature

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Abstract: Angiomyolipoma with epithelial cysts (AMLEC) is a distinctive variant of angiomyolipoma characterized by grossly apparent epithelial cysts and a cellular, müllerian-like subepithelial stroma. Some authors suspect that the epithelial cysts mainly represent dilated entrapped native renal collecting duct epithelium, while other authors think that they represented true epithelial differentiation of the AML. Recently, it has been reported that obvious immunolabeling of melanocytic markers such as Melan A and HMB45, which are often immunolabeled in classical angiomyolipoma, are present in epithelial cysts in cases of AMLEC. Here, we report the case of a 43-year-old Japanese woman with AMLEC, and attempt to elucidate the significance of melanocytic marker immunolabeling in the cyst's epithelium. In the present case, Melan A was labeled in the cyst's epithelium, and was thought to reflect its labeling in renal tubules existing in the renal parenchyma outside the tumor. This finding may indicate that the cyst epithelium is derived from entrapped renal tubules inside the AML. Non-immunolabeling of the estrogen and progesterone receptors in the cyst epithelium may also suggest that the cyst epithelium is not neoplastic, in contrast to their labeling in neoplastic cells existing in cyst wall. Further examination, such as molecular analysis, is needed to determine whether these epithelial cysts is neoplastic or non-neoplastic.

Keywords: Kidney, angiomyolipoma with epithelial cysts, Melan A, HMB45, estrogen receptor, progesterone receptor

Introduction

Angiomyolipomas (AML) are characterized by the presence of dysplastic blood vessels, smooth muscle cells with often clear cytoplasm that may be spindled or epithelioid, and fat cells similar to mature adipocytes [1]. Due to the triphasic nature of AML, it was considered as a hamartomatous lesion. However, based on the detection of clonal genomic alterations [2], AML has since been recognized as a neoplasm.

AML with epithelial cysts (AMLEC) is a distinctive variant of AML that was recently described by Fine et al. [3] and Davis et al. [4], and is characterized by grossly apparent epithelial cysts and a cellular, müllerian-like subepithelial stroma. Fine et al. speculated that the epithelial cysts mainly represented dilated entrapped

native renal collecting duct epithelium [3], whereas Davis et al. inferred that they represented true epithelial AML differentiation [4]. The pathogenesis of the müllerian-like stroma has been postulated as being caused by the embryological proximity of the urinary and genital systems [3]. These two systems commonly originate from the urogenital ridge, and it has been suggested that disturbances during a critical period in development may lead to cross-over of the epithelium or mesenchymal elements of the two systems, leading to the development of neoplasms that combine features of these systems [3].

Much more recently, Filho et al. reported obvious immunopositivity for melanocytic markers commonly expressed in classical AML in the epithelial cysts in a case of AMLEC [5]. They insisted that this is strong evidence that these

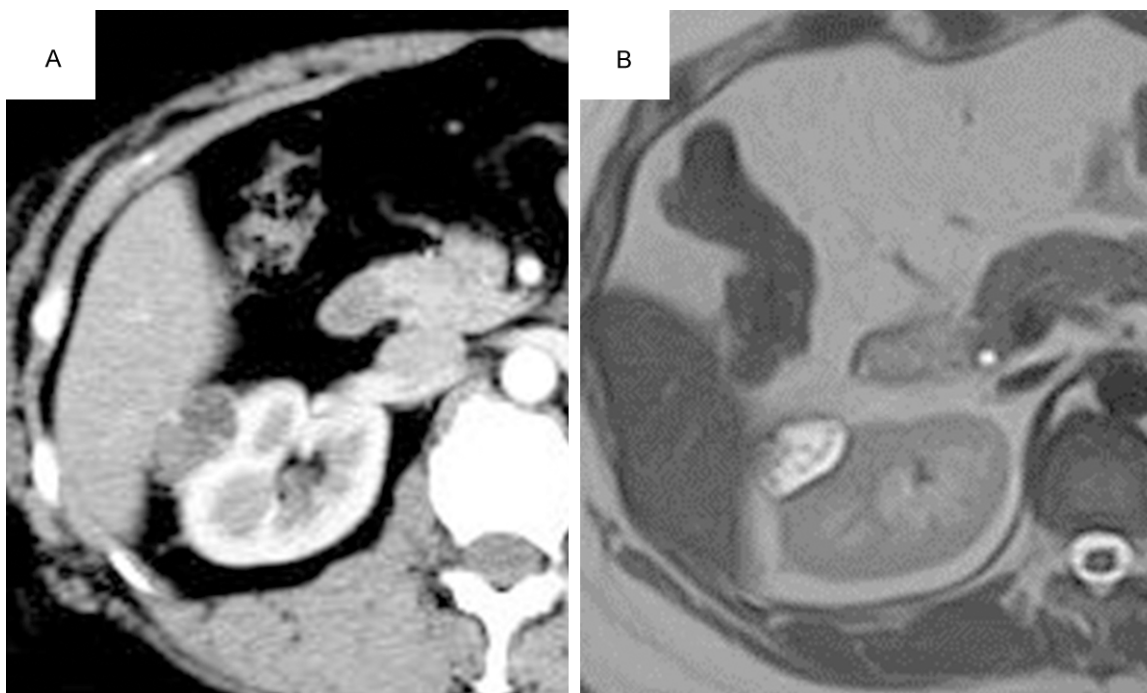


Figure 1. Radiological findings. A. On computed tomography, the cystic lesion was found at the upper part of the right kidney, and appeared as a hypovascular lesion after contrast administration; septa-like structures were observed inside the lesion. B. On magnetic resonance imaging, the lesion showed high signal intensity on T2-weighted images; septa-like structures were observed inside the lesion.

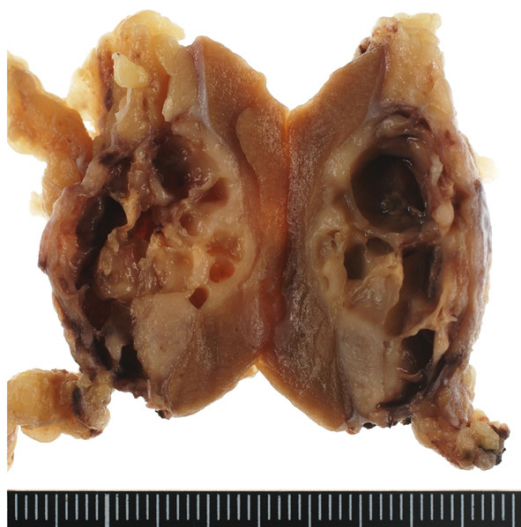


Figure 2. Macroscopic findings. The lesion was well demarcated but not encapsulated, and measured 27 × 24 × 19 mm. Multiple cysts were observed; a solid portion was identified, measuring 6 × 5 mm. The cut surface was homogeneously tan-colored.

cysts are neoplastic and derived from AML, rather than entrapped native collecting duct epithelium.

We examined whether what Filho *et al.* found in their case could be observed in ours. We present our viewpoint of the epithelial cysts in AMLEC.

Clinical summary

A 43-year-old Japanese woman presented with a right kidney lesion that was detected by ultrasonography during a check-up. She had no other complaints; physical examination and laboratory tests found no abnormalities. On computed tomography (CT), a cystic lesion was found at the upper part of the right kidney, which appeared as a hypovascular lesion after contrast administration; septa-like structures were observed inside the lesion (**Figure 1A**). On magnetic resonance imaging (MRI), the lesion showed high signal intensity on T2-weighted images; septa-like structures were observed inside the lesion (**Figure 1B**). On both CT and MRI, no solid portion was identified inside the lesion. As we were unable to decide whether the lesion was benign or malignant, partial nephrectomy was performed for both treatment and accurate diagnosis. The postoperative course was uneventful and she has been

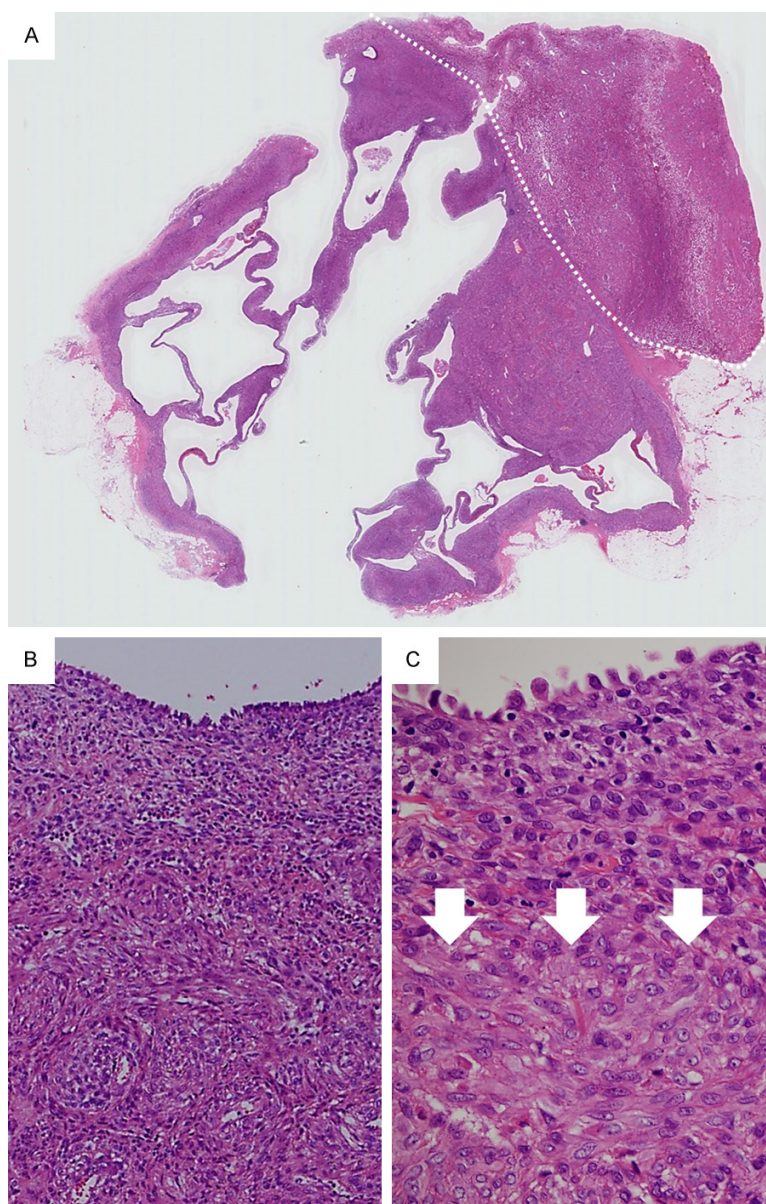


Figure 3. Microscopic findings. A. The cystic portion accounted for approximately 80% of the lesion, and the remaining 20% was the solid portion. The dotted line indicates the renal parenchyma outside the lesion ($\times 12.5$). B. The lesion was composed of the following three components: cyst epithelium, subepithelial stroma, and cyst wall ($\times 100$). C. The cyst epithelium had a hobnail appearance. The subepithelial stroma was a condensation of small stromal cells immediately subjacent to the cyst epithelium. The cyst wall was recognized as a thick exterior wall of plump smooth muscle cells (arrows) ($\times 400$).

24 \times 19 mm. Multiple cysts were observed; a solid portion was identified, measuring 6 \times 5 mm. The cut surface was homogeneously tan-colored (**Figure 2**). The lesion was predominantly located in the perirenal fat tissue, with part of it inside the kidney. Gross examination revealed no fat inside the lesion.

Microscopically, the cystic portion accounted for approximately 80% of the lesion and the remaining 20% was solid (**Figure 3A**). The lesion was composed of the following three components: 1) cyst epithelium, 2) subepithelial stroma, and 3) cyst wall (**Figure 3B**). The solid portion contained the same components as the cyst wall. In detail, the cyst epithelium ranged from cuboidal to columnar to hobnail. The subepithelial stroma was a condensation of small stromal cells immediately subjacent to the cyst epithelium. This subepithelial stroma showed signs of lymphoplasmacytic infiltrate. The cyst wall was recognized as a thick exterior wall of plump smooth muscle cells with focally clear cytoplasm arranged in poorly formed fascicles, often appearing to emanate from dysplastic blood vessels. This component was recognized as leiomyoma-like AML (**Figure 3C**). No fat was identified inside the tumor. The surgical margin was free of tumor.

recurrence-free for 1 year. She had no familial history of tuberous sclerosis.

Pathological findings

Macroscopically, the lesion was well demarcated but not encapsulated, and measured 27 \times

Immunohistochemically, we observed alpha smooth muscle actin (**Figure 4A**) and desmin labeling in the leiomyoma-like AML. HMB45 and Melan A labeling was moderate and faint in intensity, respectively, in the leiomyoma-like AML, and HMB45 labeling was stronger in the subepithelial stroma (**Figure 4B**). The cyst epi-

The nature of cysts in AMLEC

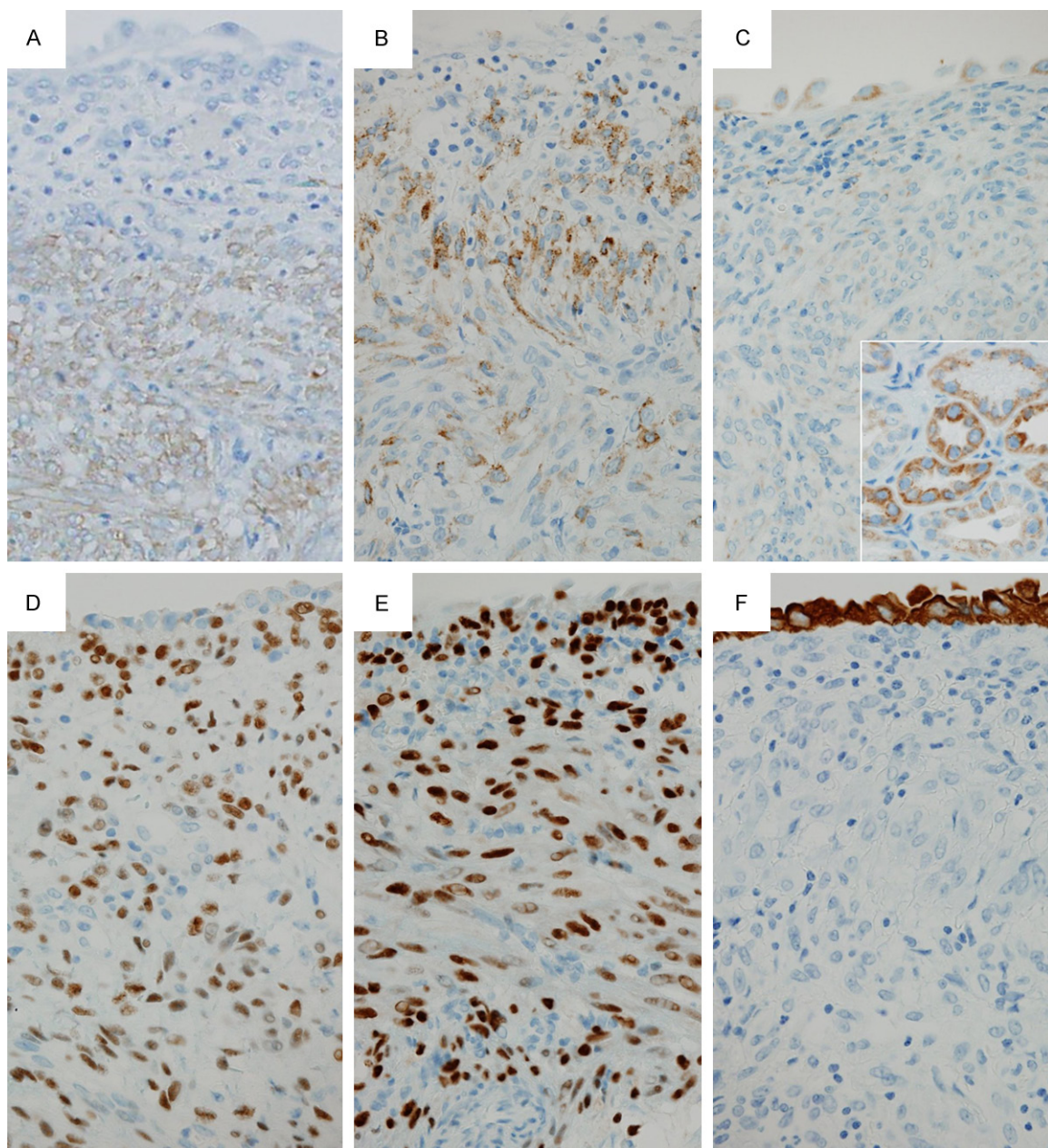


Figure 4. Immunohistochemical findings. A. Alpha smooth muscle actin labeling in the cyst wall ($\times 400$). B. HMB45 labeling in the subepithelial stroma and the cyst wall, with stronger labeling intensity in the former ($\times 400$). C. Melan A labeling in the cyst epithelium; faint labeling of Melan A in the subepithelial stroma and the cyst wall. Inset: Melan A labeling in the renal tubules in the renal parenchyma outside the tumor ($\times 400$). D. Stronger labeling for the estrogen receptor in the subepithelial stroma compared with the cyst wall; no labeling in the cyst epithelium ($\times 400$). E. Stronger labeling for the progesterone receptor in the subepithelial stroma compared with the cyst wall; no labeling in the cyst epithelium ($\times 400$). F. CK7 labeling in the cyst epithelium ($\times 400$).

thelium was labeled with Melan A (**Figure 4C**) but not HMB45. The subepithelial stroma showed strong and diffuse nuclear labeling for the estrogen receptor (ER) and progesterone receptor (PR), along with strong and diffuse cytoplasmic labeling for CD10. ER and PR label-

ing were slightly weaker in leiomyoma-like AML, and this labeling was not observed in the cyst epithelium (**Figure 4D, 4E**). The cyst epithelium was positive for AE1/3 and CK7 (**Figure 4F**). The tumor showed a low proliferative index, with Ki67 labeling of approximately 3%; howev-

er, the labeling of Ki67 was not observed in the cyst epithelium. Melan A labeling was also observed in the renal tubules in the renal parenchyma outside the tumor (**Figure 4C**, inset).

We made a diagnosis of AMLEC after reliably differentiating from other cystic lesions of the kidney, such as cystic clear cell renal cell carcinoma (RCC), multilocular cystic RCC, cystic nephroma, and mixed epithelial and stromal tumor (MEST).

Discussion

The entity most closely overlapping with AMLEC is MEST [6]. These complex tumors are characterized by cystic and solid components with variable distributions. Histologically, the stroma of MEST is often composed of well-formed smooth-muscle fascicles. Smooth muscle walls and cysts lined with epithelium often showing a hobnail appearance are common features in both AMLEC and MEST. Additionally, the stromal cells found in both AMLEC and MEST are immunolabeled with ER and PR [3, 4, 6]. However, there are several differences between AMLEC and MEST. MEST occurs predominantly in women and men with a long-term history of estrogen exposure [6]. In contrast, AMLEC often occurs in men without a history of exogenous hormone exposure [4]. Moreover, the vessels found in cases of AMLEC are dysplastic, in contrast to those found in cases of MEST. Finally, smooth muscle cells in the cyst wall in cases AMLEC form less well-developed fascicles, are more epithelioid, and often have clearer cytoplasm than those found in MEST; smooth muscle cells in AMLEC and MEST are positive and negative for melanocytic markers, such as HMB45 or Melan A, respectively [3, 4, 6]. In the present case of a female patient, the morphological and immunohistochemical features of the smooth muscle cells allowed us to make a reliable diagnosis of AMLEC.

The epithelial component in MEST is considered to be either neoplastic [7] or non-neoplastic [8]; both are still possible. ER and PR immunolabeling only in the mesenchymal component in MEST may indicate the non-neoplastic nature of the epithelial component [8]. In AMLEC, the cyst epithelium has been described as immunonegative for ER and PR [3, 4]. This fact may

indicate that the cyst epithelium is non-neoplastic in AMLEC.

Recently, Filho *et al.* stated that the cyst epithelium in AMLEC is neoplastic because melanocytic markers, such as Melan A and HMB45, are immunolabeled in the cyst epithelium, with the former showing diffuse labeling and the latter showing focal labeling [5]. However, the immunohistochemical features of the cyst epithelium were initially described as follows: strong reactivity to pancytokeratin, focal expression of soy bean agglutinin (a marker of distal nephron epithelium), and no expression of the melanocytic markers, ER, PR, CD10, and renal cell carcinoma antigen as reported by Fine *et al.* [3]. A similar pattern of immunolabeling in the cyst epithelium has been reported in two additional cases [9, 10]. There has never been a case like that described by Filho *et al.*, with the cyst epithelium immunolabeled with melanocytic markers. They used Melan A (clone: A103; Dako) and HMB45 (clone: HMB45; Dako); Fine *et al.* probably used different antibodies purchased from Ventana (Tucson, AZ), and the clone names were not described [10]. Of the abovementioned two additional cases, one did not contain detailed antibody information [9] and the other contained such information but examined only HMB45 (clone: HMB45; Dako) [10]. In the present case, we used the same antibody as Filho *et al.* Although HMB45 labeling was not identified, Melan A was diffusely immunolabeled in the cyst epithelium as reported previously [5]. However, we noticed that the renal tubules in the renal parenchyma outside the AMLEC were immunolabeled with Melan A. We suspected that Melan A labeling in the cyst epithelium reflected this immunolabeling in renal tubules. This theory is supported by the observation of faint Melan A labeling in the neoplastic smooth muscle cells; a discrepancy of labeling intensity existed between the cyst epithelium and smooth muscle cells of AMLEC in our case. Therefore, Melan A labeling in the cyst epithelium cannot be interpreted as representing similar cyst epithelium differentiation to that exhibited by Melan A-labeled subepithelial stroma and smooth muscle cells in the cyst wall. We therefore think that further evidence is needed to demonstrate that the epithelial component in AMLEC is neoplastic. At present, we propose that the epithelial component is comprised of

non-neoplastic, entrapped, and dilated renal tubules as described by Fine *et al.* [3].

In conclusion, the cyst epithelium in AMLEC has not yet been determined to be neoplastic or non-neoplastic. Melan A labeling in the cyst epithelium supposedly reflects its labeling in renal tubules, and may indicate that the cyst epithelium is derived from entrapped renal tubules inside the AML. Non-immunolabeling of ER and PR in the cyst epithelium may also suggest that the cyst epithelium is not a neoplastic element in contrast to their expression in the neoplastic element, such as smooth muscle cells in the cyst wall. Further examination, such as molecular analysis, is needed to confirm whether these epithelial cysts are neoplastic or non-neoplastic.

Disclosure of conflict of interest

None

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