Case Report

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Giant Angiomyolipoma with Epithelial Cyst (AMLEC): Case Report and Review of Literature

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Abstract

Angiomyolipoma with epithelial cyst (AMLEC) is a rare variant of angiomyolipoma (AML). Hereby, we report a unique case which is the largest size of AMLEC ever reported, the patient being the youngest one ever recorded, and the first case of AMLEC associated with tuberous sclerosis complex reported from India. The patient was a 19-year-old woman who presented with hematuria. Contrast-enhanced computed tomography (CT) and positron emission tomography-CT detected a large complex cystic lesion, which was reported to be AML with a less likely possibility of cystic renal cell carcinoma. The patient underwent radical nephrectomy. Histopathology and immuno-histochemistry identified the tumor to be AMLEC. On further evaluation, the patient was found to satisfy clinical criteria of tuberous sclerosis complex. Rare forms of renal tumor like AMLEC need to be kept in mind whenever we encounter complex cystic lesions in the kidney.

Keywords: Angiomyolipoma with epithelial cyst, angiomyolipoma, renal tumor, renal cyst, tuberous sclerosis complex

Introduction

Angiomyolipoma (AML) is a member of a tumor family known as perivascular epithelioid cell (PEC) tumors which originate from the histologically, ultra-structurally and immunohistochemically distinctive PEC (1). AML is easily picked up on ultrasound by virtue of hyperechogenicity generated by its fat content and negative Hounsfield units on unenhanced computed tomography (CT). A rare form of AML, like AML with epithelial cyst (AMLEC), often mimics more sinister pathology due to its solid-cystic nature. Moreover, AMLEC does not readily come to the mind of clinicians due to its rarity (2). It is a relatively new entity, and it is difficult to segregate it from common lesions like mixed epithelial stromal tumor (MEST), cystic nephroma (CN) and even cystic renal cell carcinoma (RCC), both clinically and histologically (2,3). We report a case of AMLEC, which is the first of its kind from multiple perspectives, and a review of relevant literature is incorporated.

Case Reports

1. Case history and clinical findings: A 19-year-old female presented with left flank pain and intermittent painless visible hematuria for 2 months. On examination, she was pale and there was a palpable left renal mass.

2. Imaging findings: Multiphasic CT showed a normal right kidney. In the left kidney, there was a well-defined fat-attenuating partly exophytic, 10x10 mm sized lesion at the lower pole, diagnosed as AML. A second lesion, 3.4 mm sized, rounded non-enhancing fat attenuating lesion in the interpolar region, was diagnosed as AML. A third fairly large, upper polar, solid cystic lesion measuring 18.4x15x9.5 cm including a cystic component of size 5.4x5.2x5.0 cm was also observed. There were multiple enhancing septa of thickness up to 3 mm in the cyst (Bosniak IV). The lesion produced a bulge on the lateral aspect of the kidney with protrusion into perirenal fat, without loss of the fat plane. There was a linear non-occlusive poorly enhancing filling defect, measuring 38x12 mm, in the hilar

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region of left renal vein, and the radiologist considered it to be a possible tumor thrombus. CT considered differentials of large AML or fat-containing RCC. CT also reported a 22x21 mm sized, enhancing lesion with persistent post-contrast enhancement, hence labeled as a hemangioma in segment VIII of the liver. Further work-up of the renal mass with positron emission tomography (PET)-CT revealed a large ametabolic solid-cystic, predominantly fat containing lesion in the left kidney, and was considered to be a fat-rich AML (4).

3. Surgical findings: The patient was subjected to left radical nephrectomy. The cut section of the specimen showed an upper polar large tumor mass, measuring 19x15x10 cm, which was pale yellow, solid and homogeneous, and had a cyst in the parapelvic region (Figure 1).

4. Pathology findings: On histology, it was found to be a triphasic tumor composed of (a) myoid spindle cells without any atypia, pleomorphism or epithelioid features, (b) mature adipose tissue and (c) dysmorphic thick-walled blood-vessels without elastic lamina.

The cystic spaces were lined with cuboidal to columnar epithelium having eosinophilic cytoplasm and prominent nuclei protruding into the lumen (hobnailed appearance). There was condensation of small stromal cells (cambium-like) with congested capillaries and lymphoplasmacytic infiltrate in the subepithelial layer (Figure 2). Fascicles of smooth muscle bundles with entrapped, non-cystic native renal tubules were arranged in the external 3rd layer.

This was a characteristic picture of AMLEC as described in the literature. The renal sinus, renal artery and vein, renal capsule, ureter, and peri-renal fat were not involved by the tumor.

5. Immuno-histochemistry: Considering rarity of AMLEC, the specimen was subjected to immuno-histochemistry. The subepithelial layer was strongly positive for HMB45. Smooth muscle actin (SMA) stain produced a strong reaction in the outer muscular layer (Figure 3), and S100 was negative, thereby

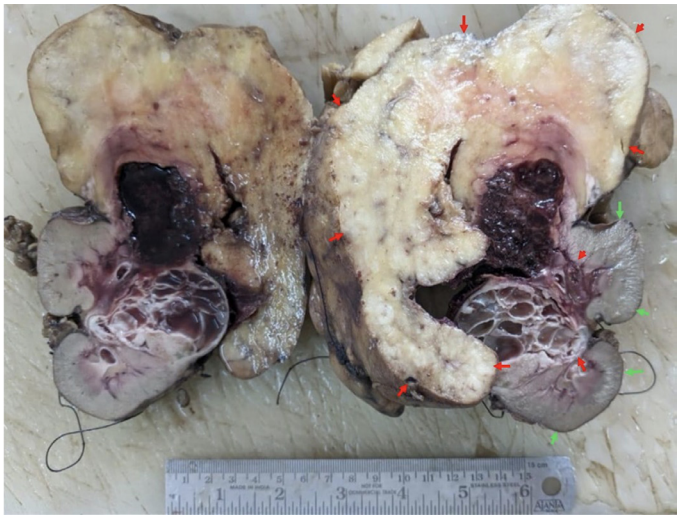

Figure 1. Cut section of nephrectomy specimen showing tumor (red arrows), left kidney (green arrows) and fluid-filled cyst in between. For estimation of dimensions, a metallic scale was placed at the bottom

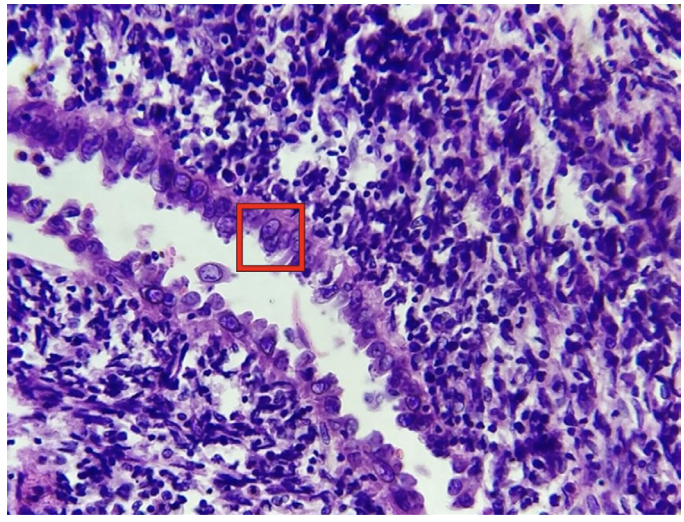

Figure 2. Microphotograph of H&E-stained slide showing cyst wall lined by hob-nailed epithelium (red rectangle); condensed "cambium-like" subepithelial stroma with multiple vessels and lymphoplasmacytic infiltrate is seen

H&E: Hematoxylin and eosin

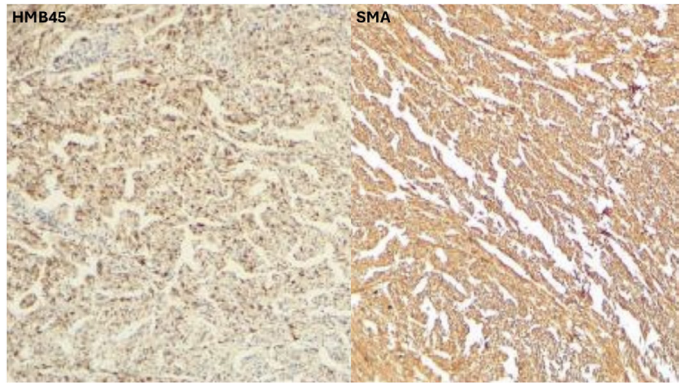

Figure 3. Strongly positive reaction with HMB45 stain (left half) and smooth muscle actin stain (right half) is seen

SMA: Smooth muscle actin

confirming the diagnosis of AMLEC. The proliferation index Ki-67 was <1%.

After reviewing the literature on AMLEC, the patient was again evaluated. She was found to be meeting one major (multiple AMLs) and two minor criteria (hepatic hamartoma and "confetti" skin lesions) of tuberous sclerosis complex (TSC).

Discussion

AMLEC as an entity was recognized in the recent past, and reports appeared in the literature in the past 2 decades. Although the description of cystic AML with HMB45 positive subepithelial stroma given by Davis et al. (5) was very close to that of AMLEC, the first accurate description of AMLEC was given by Fine et al. (6). It is believed that, in fact, some of the previously reported cases of fat-containing RCC carcinoma were AMLECs. Awareness among urologists is desired because clinically AMLEC closely mimics other complex cystic lesions, especially cystic RCC and histologically MEST (2,3).

AMLEC is a late addition to the list of cystic renal tumors, which previously included cystic RCC, CN and MEST (Table 1). It is known that entrapped renal tubules can be seen in the histological architecture of AML under a high-resolution microscope, but they never undergo gross dilatation to form cysts (2). AMLEC needs to be differentiated from cystic RCC. Histological features which segregate AMLEC from RCC are the absence of clusters of clear cells and papillary carcinoma cells, the single-layered clear cell epithelial lining of the cyst wall, necrotic debris, cholesterol clefts, and calcification. It has been suggested that the cyst of AMLEC originated from the epithelium of collecting ducts because of positive immunoreactivity for soybean agglutinin (2), in contrast to the origin of RCC from the epithelium of the proximal renal tubule. Hence, AMLEC does not stain with the RCC marker. Cuboidal or columnar epithelium with clear or eosinophilic cytoplasm and prominent nuclei projecting into the lumen of cyst (hob-nail appearance) is surrounded by mullerian-type endometrium-like highly vascular stroma infiltrated by lymphoplasmacytic infiltrate forming a layer of so-called "cambium". An outer layer of fascicles of muscular stroma with dysplastic vessels is characteristic and unmistakable in AMLEC (2,3,6). Cysts lined by cuboidal or hob-nailed epithelium are common to AMLEC, CN, and MEST. The stroma in CN is sparse and ovarian-type, unlike the thick, condensed endometrial stroma of AMLEC. Characteristic features of AMLEC, e.g., condensed sub-epithelial cambium-like stroma, thick muscular outer layer, and dysmorphic vessels are absent in CN (2,3,7). MEST can have solid-cystic components, but thick-walled blood vessels of MEST are distinctly different from dysmorphic blood vessels of AMLEC (2). Micro and macro-cystic spaces are a feature of MEST compared to the large cysts of AMLEC. SMA, desmin and ER/PR can be positive in both AMLEC and MEST, but melanocytic markers like HMB45 and Melan-A, which are features of PEC, form the line of demarcation between AMLEC and MEST. Markers of immunohistochemistry are not mono-specific, but a battery of multi-specific markers does help in recognizing the exact cell lineage of the lesion in the present case (Table 2). Since the patient is young, we need to differentiate the lesion from cystic poorly differentiated nephroblastoma (CPDN), but CPDN occurs before age 2. Typical nephroblastomatous epithelial and stromal elements along with blastema of CPDN are absent in our case (2). The present case needs to be differentiated from epithelioid AML (eAML) because of young age, its association with TSC, positivity for HMB45 and SMA, and negative reaction for S100. Typical features of eAML like epithelioid cells, nuclear atypia, and mitotic figures were absent in the present case. Secondly, proliferative index, Ki-67, which was reported to be <1%, in our case, rules out the possibility of eAML (8).

Pre-operatively, this patient had shown heterogeneous enhancement on contrast-enhanced CT although unenhanced CT had demonstrated fat. Heterogeneous enhancement can occur in fat-poor AML and non-clear cell RCC both, raising suspicion (4). Unusual size of tumor and heterogeneous

Table 1. Histological differentials of complex renal lesion

Kidney lesion	Cyst	Characteristic features	
		Epithelium	Stroma
Cystic RCC	Present	Nests of clear cells or papillary carcinoma cells; Cyst wall lined by single layered clear cell epithelium with distinct membrane	Non-descript with little inflammatory response; Haemorrhage, necrotic debris, cholesterol clefts, Calcification; Network of arborizing thin-walled blood-vessels
AMLEC	Present	Cuboidal or columnar epithelium with clear or eosinophilic cytoplasm with prominent nuclei projecting into the lumen of cyst (hob-nail appearance) is common to AMLEC, CN and MEST	Mullerian-type endometrium-like highly vascular "cambium'-like" stroma infiltrated by lymphoplasmacytic infiltrate; Outer thick muscular layer with dysmorphic blood-vessels
CN	Present		Sparse, ovarian type stroma
MEST	Present		Thick-walled blood-vessels seen in stroma
CPDN	Present	Nephroblastomatous	Nephroblastomatous stroma and Islands of undifferentiated blastema
AML	Entrapped renal tubules may be seen under high resolution but there is no gross dilatation to form cyst		

AMLEC: Angiomyolipoma with epithelial cyst, AML: Angiomyolipoma, RCC: Renal cell carcinoma, MEST: Mixed epithelial stromal tumour, CN: Cystic nephroma, CPDN: Cystic poorly differentiated nephroblastoma

Table 2. Immunostaining findings in various complex cystic lesions of kidney

Type of lesion	Immunoreactive antibody				
	Cytokeratin	S100	HMB45	Melan-A	SMA
Cystic RCC	+ve	+ve	-ve	-ve	-ve
AMLEC	-ve	-ve	+ve	+ve	+ve
MEST	+ve	-ve	-ve	-ve	+ve
CN/CPDN	+ve	-ve	-ve	-ve	+ve
AML	-ve	-ve	+ve	+ve	+ve

SMA: Smooth muscle actin, AMLEC: Angiomyolipoma with epithelial cyst, AML: Angiomyolipoma, RCC: Renal cell carcinoma, MEST: Mixed epithelial stromal tumour, CN: Cystic nephroma, CPDN: Cystic poorly differentiated nephroblastoma

enhancement are indicative for the use of magnetic resonance imaging (MRI) in differentiating fat-poor AML from a malignant lesion. Based on MRI findings, AML is classified into 3 categories, namely fat-rich, fat-poor, and fat-invisible. Fat-rich AML needs no further work-up; fat-poor AML can be differentiated from non-clear cell RCC by using MRI, but MRI findings are similar in fat-invisible AML and malignant lesions. If MRI does not help in diagnosis, percutaneous biopsy is indicated (4). In our case, we preferred to confirm AML by PET-CT, which revealed a metabolic lesion, because AML is not fluorodeoxyglucose-avid, unlike malignant lesions which show FDG uptake. The heterogeneous enhancement in the present case, was due to the tumor being fat-poor, just like any other AMLEC and unlike the majority of AMLs, which are usually fat-rich.

To date, a total of 28 cases of AMLEC have been reported in 12 publications worldwide (9). This patient is just 19 years old and is the youngest ever to have AMLEC. Before this, the youngest patient of AMLEC ever reported was 23 years old (10). If the lesion in our case is considered sporadic AML or its variant, then how could it grow to this size by the age of 19 years? This idea forced us to think about whether the patient belongs to some familial neoplastic syndrome, associated with renal tumor. This patient fulfills one major criterion (multiple AMLs) and two minor criteria (hepatic hamartoma and confetti skin lesion) of TSC (11). AML in TSC usually occurs in the 3rd or 4th decade of life (3). Secondly, this lesion is the biggest AMLEC ever noticed, far bigger than the commonly reported size in the literature. If this case is accepted as AMLEC in TSC, then this is the first case from India in that category.

As of today (2,9,12), there is no tumor marker or imaging modality that can diagnose AMLEC preoperatively. There is no standardized treatment for AMLEC because of its rarity. In the literature, partial nephrectomy is recommended if size is up to 5 cm, it beyond which it is indicated that radical nephrectomy is necessary (2). There is no role of chemotherapy or radiotherapy as of now. Inactivation of tumor suppressor gene TSC2 due to a non-sense mutation, which results in unregulated signaling of the mammalian target of rapamycin (mTOR) complex 1 pathway, has been proposed to be the causative mechanism in TSC-associated AMLEC (9). Based on this finding, mTOR inhibitor everolimus has been suggested as an adjunct in the treatment of AMLEC (9). In fact, cell-lines of all renal tumors need to be defined very precisely, to maximize the benefit from fast emerging molecular biology-based targeted therapeutic options. Clinically, the behavior of AMLEC is no different from AML, it has never been found to recur or metastasize; and it has never been blamed for mortality (2).

Ethics

Informed Consent: Treatment of this patient was in accordance with standard urological protocol. The operation was carried out after obtaining the patient's written informed consent, as is required for invasive procedures in our institution. For academic purposes, permission from the Institutional Review Board was obtained, and a waiver of consent for publication from the patient was granted, as the patient's identity was not disclosed for review of records and publication.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Design: M.P., P.L., R.H., Data Collection or Processing: P.M., Literature Search: M.N., Writing: E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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