

## Angiomyolipoma with Epithelial Cysts: A Case Report and Review of Literature

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### ABSTRACT

Angiomyolipoma with epithelial cysts (AMLEC) is a rare subtype of angiomyolipoma that may closely mimic both malignant and benign neoplasms. We report a case of AMLEC in an 18-year-old female presenting with acute flank pain and radiologic suspicion for malignancy. This case highlights the diagnostic challenges posed by AMLEC, emphasizes its characteristic histopathologic and immunohistochemical features, and reviews current concepts regarding its pathogenesis. This case represents the first documented case of AMLEC in the Philippines.

**Key words:** *angiomyolipoma, angiomyolipoma with epithelial cysts, kidney neoplasms, histopathology, immunohistochemistry, case report*

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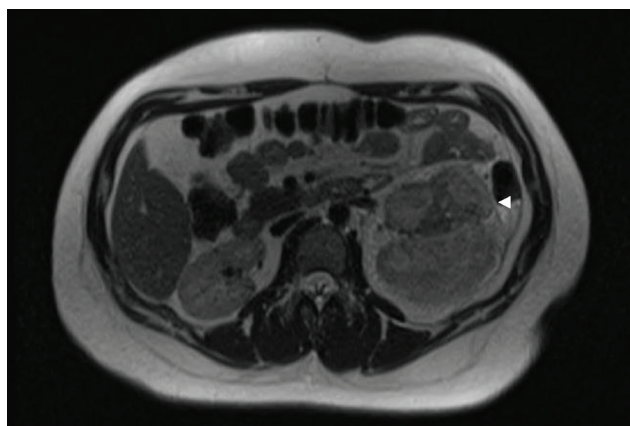
### INTRODUCTION

Angiomyolipoma with epithelial cysts (AMLEC) is recognized as a rare subtype of renal angiomyolipoma (AML) by the World Health Organization (WHO) Classification of Tumors.<sup>1</sup> Unlike classic AML, AMLEC is characterized by a complex admixture of solid and cystic components, a feature that may pose a diagnostic challenge due to its ability to closely mimic both benign and malignant renal neoplasms on imaging and histopathologic examination. Since its initial description in 2006,<sup>2,3</sup> only a limited number of cases have been reported in the literature, and its pathogenesis remains incompletely understood. This case report aims to describe the clinicopathologic features of AMLEC, highlight the diagnostic utility of immunohistochemistry in distinguishing it from its benign and malignant mimics, and discuss current theories regarding its pathogenesis. To the authors' knowledge, this represents the first reported case of AMLEC in the Philippines, and one of the youngest patients described in literature.

### CASE

We present the case of a previously healthy 18-year-old female who was brought to the emergency department due to sudden onset left flank pain. Patient had no comorbid diseases, and no family history of tuberous sclerosis complex. Magnetic resonance imaging (MRI) revealed a heterogeneous mass in the anterior interpolar to inferior pole of the left kidney with an exophytic component measuring 3.9 x 4.3 x 3.6 cm (Figure 1). Also noted was a heterogeneous fluid collection representing hyperacute to acute subcapsular renal hemorrhage. The primary radiologic consideration at this time was a renal cell carcinoma associated with hemorrhage secondary to spontaneous rupture. The patient subsequently underwent left open radical nephrectomy. On gross examination, there was note of a cream tan to brown, firm to rubbery solid mass with irregular contour measuring 4 x 3.5 x 2.5 cm in single widest dimension, located predominantly within the perinephric fat of the middle to inferior pole of the kidney, with involvement of the renal cortex on sectioning.



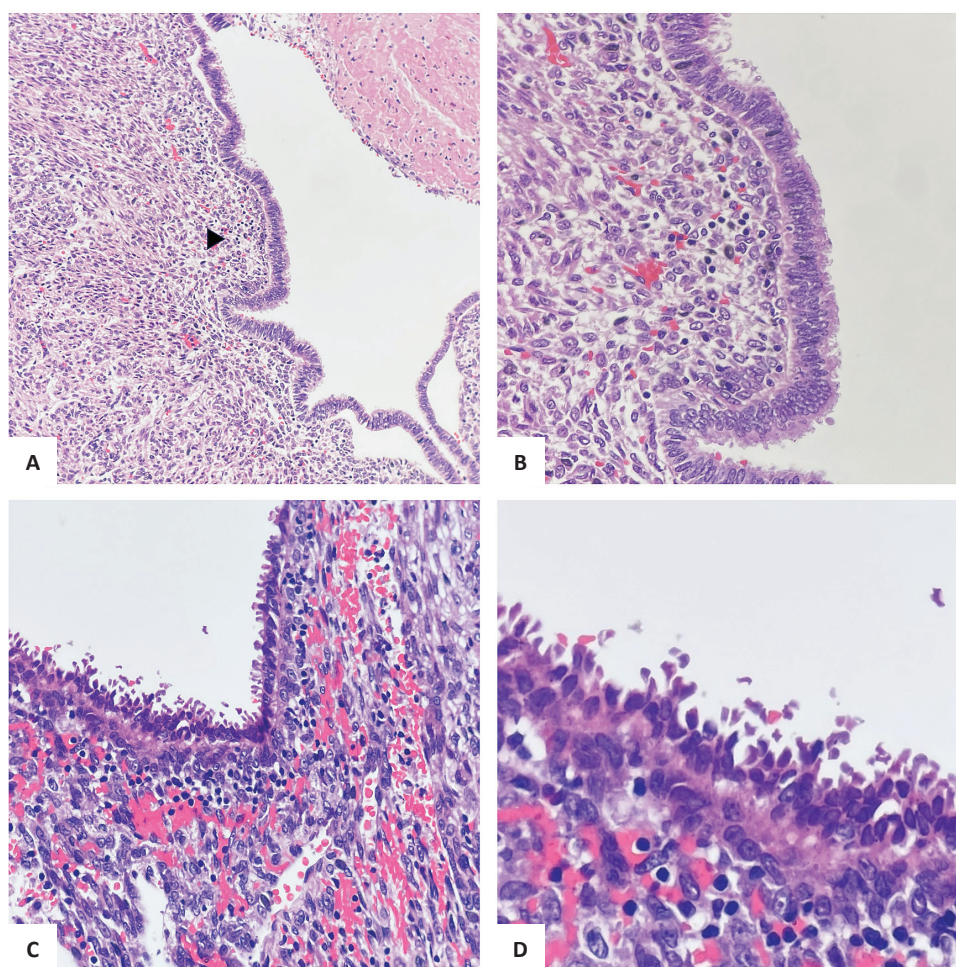


**Figure 1.** MRI of the upper abdomen showing a heterogeneous mass in the left kidney (*arrowhead*).

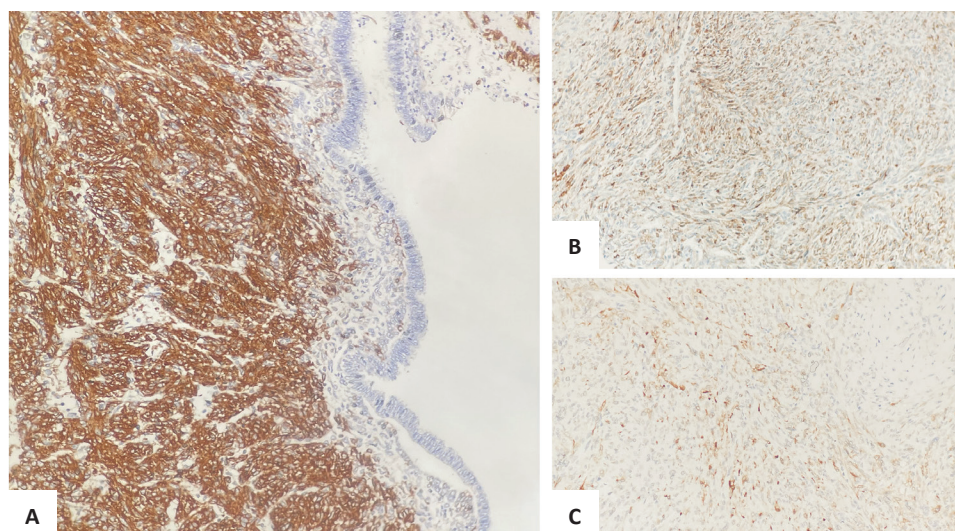
Microsections of the mass disclosed plump spindle cells arranged in solid sheets, associated with thick-walled, dysmorphic blood vessels, and focal areas of mature adipose tissue, morphologically consistent with classic AML. Interspersed between these areas were multiple varisized cysts lined by bland-appearing cuboidal to columnar cells, with some exhibiting hobnailed appearance. These cystic

structures were embedded in a cellular, cambium-like stroma composed of small, compact round to spindle cells with scant cytoplasm, associated with lymphocytic infiltrates (Figure 2).

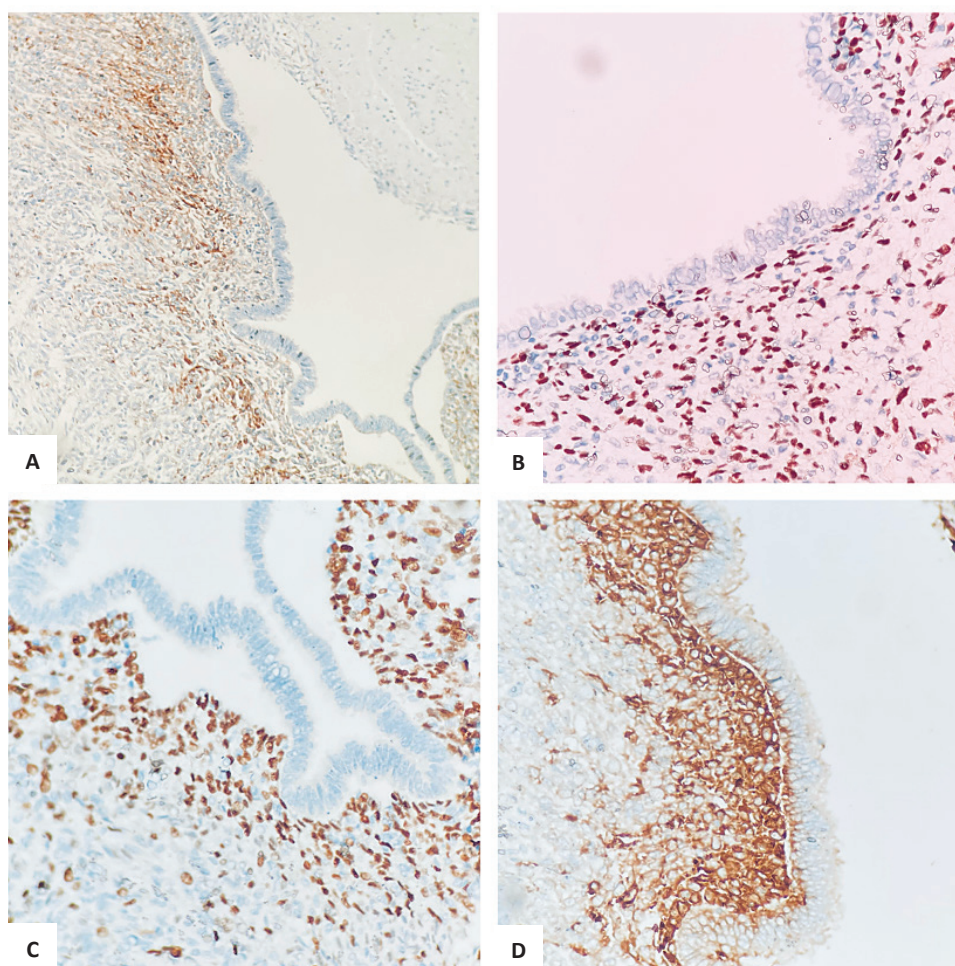
Immunohistochemical studies (Table 1) were performed for a more definite diagnosis and to rule out benign and malignant differentials. The solid, spindled areas showed positive, patchy expression for melanocytic markers human melanoma black (HMB45) and Melan A, while smooth muscle actin (SMA) showed diffused positivity, consistent with a smooth muscle-predominant AML (Figure 3). The cambium-like stroma exhibited positive staining for melanocytic markers, with particularly strong staining for HMB45 relative to the smooth muscle-predominant area (Figure 4A). In addition, the cambium-like layer strongly expressed estrogen receptor (ER), progesterone receptor (PR), and cluster of differentiation 10 (CD10) (Figure 4B to 4D). The cyst-lining cells stained positive for cytokeratin, demonstrating their epithelial origin (Figure 5A). Additionally, these cells showed positive staining for paired box 8 transcription factor (PAX8) (Figure 5B) and negative staining for melanocytic markers, ER, and PR (Figure 4A to 4C). Based on these findings, a diagnosis of AMLEC was rendered.



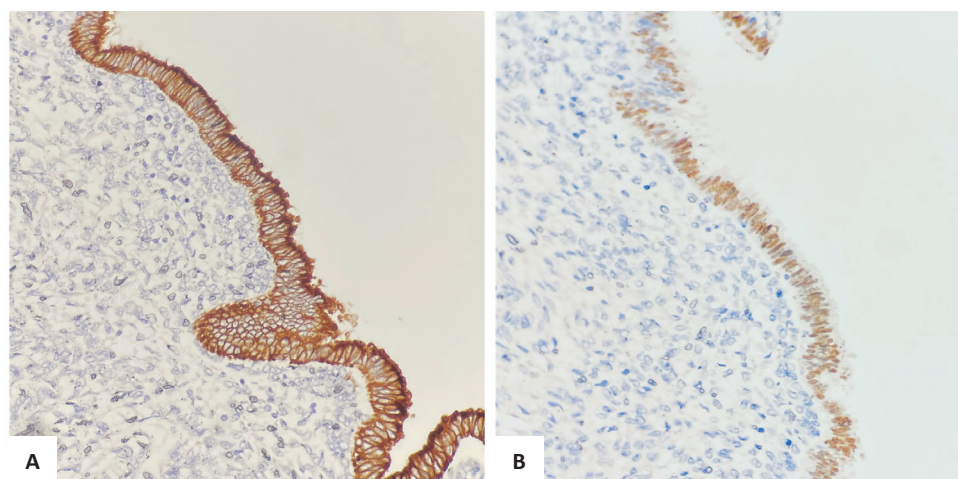
**Figure 2.** Cysts lined by columnar to cuboidal cells embedded in a cambium-like stroma (*arrowhead*) (A) H&E, 100x (B) H&E, 200x. Cyst-lining cells exhibiting hobnailed appearance (C) H&E, 200x (D) H&E, 400x.



**Figure 3.** Spindle cell component of tumor with positive staining for **(A)** SMA, 200x, **(B)** HMB45, 200x, and **(C)** Melan A, 200x, with note of negative expression of SMA in the subepithelial stroma **(A)**.



**Figure 4.** Cambium-like subepithelial stroma with positive staining for **(A)** HMB45, 200x, **(B)** ER, 200x, **(C)** PR, 200x, **(D)** CD10, 200x, and negative staining in cyst-lining cells.



**Figure 5.** Cyst-lining cells showing positive staining for (A) CK, 200x and (B) PAX8, 200x.

**Table 1.** Summary of immunohistochemical stain results

| Immunohistochemical Stain | Spindle cell-predominant area | Cyst-lining cells     | Cambium-like stroma |
|---------------------------|-------------------------------|-----------------------|---------------------|
| <b>CK</b>                 | Negative                      | Positive              | Negative            |
| <b>PAX8</b>               | Negative                      | Positive              | Negative            |
| <b>SMA</b>                | Positive, strong, diffuse     | Negative              | Negative            |
| <b>HMB45</b>              | Positive                      | Negative              | Positive, strong    |
| <b>Melan A</b>            | Positive                      | Negative              | Positive            |
| <b>ER</b>                 | Negative                      | Negative              | Positive            |
| <b>PR</b>                 | Negative                      | Negative              | Positive            |
| <b>CD10</b>               | Negative                      | Positive, weak, focal | Positive            |

CD10, cluster of differentiation 10; CK, cytokeratin; ER, estrogen receptor; HMB45, human melanoma black; PAX8, paired box 8 transcription factor; PR, progesterone receptor; SMA, smooth muscle actin

**Table 2.** Comparison of clinical and demographic features of present and previously reported cases

| Feature                           | Previously reported cases <sup>2,3,5-18</sup> (36 patients)                         | Present case                                               |
|-----------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------|
| <b>Age (years)</b>                | 17-76 (Median 41.5)                                                                 | 18                                                         |
| <b>Sex</b>                        | Female predominance (67%)                                                           | Female                                                     |
| <b>Clinical presentation</b>      | Incidental findings (52%)<br>Others: Flank pain, hematuria, dysuria                 | Flank pain                                                 |
| <b>Laterality</b>                 | Unilateral (Right = Left)<br>Bilateral in one case <sup>3</sup>                     | Left                                                       |
| <b>Size (cm.)</b>                 | 1.3-11 (Median 3)                                                                   | 4                                                          |
| <b>Tuberous sclerosis complex</b> | Three cases: 17/Male <sup>5</sup> , 37/Female <sup>3</sup> , 46/Female <sup>6</sup> | No personal or family history                              |
| <b>Outcome</b>                    | Alive with no disease recurrence                                                    | Alive with no evidence of disease at most recent follow-up |

Following surgery, the patient had an unremarkable postoperative course and was discharged stable. At the most recent follow-up, patient was clinically well with no evidence of disease.

## DISCUSSION

AMLEC is a rare subtype of renal AML exhibiting cystic and solid architecture, in which epithelial-lined cysts surrounded by a cambium-like stromal layer are admixed with a predominantly smooth muscle-rich angiomyolipomatous component.<sup>1-4</sup> The characteristic histopathologic features of this entity were first described in 2006 by Davis et al.,<sup>2</sup> in a series of 11 cases, while in the same year, Fine et al.,<sup>3</sup> formally designated the lesion as angiomyolipoma with epithelial cysts, or AMLEC.

Based on a review of published literature<sup>2,3,5-18</sup> (Table 2), fewer than 40 histopathologically well-documented cases of AMLEC have been reported, with additional isolated cases described in clinically or radiologically focused publications. Reported cases of AMLEC span a wide age range, from 17 to 76 years, with a median age of 41.5 years among the cases reviewed. A female predominance was observed, and tumors most commonly arose unilaterally, with no clear predilection for the right or left kidney. One case demonstrated bilaterality;<sup>3</sup> however, histopathologic confirmation was done for only one kidney. Tuberous sclerosis complex was identified in only three patients,<sup>3,5,6</sup> diagnosed at 17, 37, and 46 years of age, with all tumors occurring unilaterally. Notably, one patient with tuberous sclerosis complex was found to have an associated eosinophilic solid and cystic renal cell carcinoma and epithelioid AML in the same kidney.<sup>6</sup> Consistent with

literature, our patient is female with a unilateral tumor; however, at 18 years of age, she represents one of the youngest reported cases, and the youngest case with no personal or family history of tuberous sclerosis complex. AMLEC has most commonly been reported as an asymptomatic incidental finding on imaging performed during routine medical examinations or evaluation for unrelated conditions,<sup>2,4</sup> in contrast to our patient who presented with sudden onset flank pain. When symptomatic, presenting features have included flank pain,<sup>2,3,7,8</sup> hematuria,<sup>2,3,9</sup> dysuria,<sup>3,7</sup> and less commonly, groin pain,<sup>3</sup> chronic renal insufficiency,<sup>3</sup> and acute abdomen from retroperitoneal hemorrhage.<sup>2</sup> Radiologically, AMLEC typically appears as a solid or complex cystic mass,<sup>4</sup> as opposed to most classic AMLs which exhibit high fat content on ultrasonography and computed tomography.<sup>1</sup> Owing to its nonspecific imaging characteristics, AMLEC has been reported to mimic renal cell carcinoma,<sup>3,7,10-13</sup> resulting in radical surgical management. In the present case, although renal cell carcinoma was similarly the primary clinical and radiologic consideration, the presence of acute subcapsular hemorrhage was a factor that influenced the decision to proceed with radical surgical intervention in the context of tumor-associated bleeding. Following resection, AMLEC was grossly described in literature as a well-circumscribed, yellow to gray, solid to cystic mass, with sizes ranging from 1.3 cm. to 11 cm.,<sup>2,3,5-18</sup> the largest of which was reported by Varshney et al.<sup>7</sup> In this patient, the tumor was predominantly solid on gross examination, and fell within the reported size range.

Microscopically, AMLEC is characterized by three distinct features, namely, a smooth muscle-predominant angiomyolipomatous component, epithelial-lined cysts, and a compact, subepithelial cambium-like stromal layer.<sup>1-3</sup>

The smooth-muscle predominant AML accounts for the solid areas of the tumor, and is composed of sheets or fascicles of plump spindle cells arising from thick-walled vessels, and scant to absent adipose tissue.<sup>2,4</sup> These typically stain positive for SMA and the melanocytic markers HMB45 and Melan A, consistent with the immunohistochemical profile of a smooth muscle-predominant AML.<sup>2,4</sup>

The subepithelial layer immediately beneath the epithelial-lined cysts is composed of small, compact spindle cells with scant cytoplasm, forming a cambium-like pattern that is sharply demarcated from the surrounding smooth muscle component.<sup>2,4</sup> Immunohistochemically, this cambium-like stromal layer shows strong expression of melanocytic markers, compared to the adjacent smooth muscle stroma where staining is less intense. It also typically expresses ER, PR, and CD10. Together with its morphologic resemblance to endometrial stroma and distinct immunoprofile, this stromal component has been interpreted as exhibiting features of both Müllerian and melanocytic differentiation.<sup>3,4,10</sup> In the literature, Müllerian differentiation in renal neoplasms has been attributed to the shared embryologic origin of the urinary and genital systems from the urogenital ridge, resulting in overlapping epithelial and mesenchymal differentiation between the two systems.<sup>3-4,10</sup> This cambium-like layer is considered a defining feature of AMLEC that distinguishes it from other cystic renal neoplasms.<sup>2,4</sup>

The epithelial cysts are described as variably sized and lined by bland-appearing cuboidal to columnar cells with eosinophilic to clear cytoplasm.<sup>2,4</sup> Some exhibit hobnail morphology, with nuclei protruding into the cystic lumen.<sup>2,4</sup> These cyst-lining cells typically stain positive for pancytokeratins, thereby supporting their epithelial nature, and are negative for melanocytic markers, as well as ER, PR, and CD10.<sup>2,4</sup> The origin of these epithelial cells, however, is a subject of contention, with two possible theories discussed in literature. One was proposed by Fine et al.,<sup>3</sup> who theorized that the cysts come from dilated entrapped native tubules because of their morphologic resemblance to collecting duct epithelium. Obstruction of these tubules by the AML is said to result in dilatation and cyst formation.<sup>3</sup> This mechanism is favored by a number of subsequent case reports.<sup>13,14</sup> Notably, a study by Karafin et al.,<sup>5</sup> further supported this theory by demonstrating similar PAX2 and PAX8 positivity between epithelial cysts of AMLEC and renal tubules of benign kidney tissue. In contrast, Davis et al.,<sup>2</sup> argued against entrapment of renal tubules as the origin, stressing that entrapped tubules are typically confined to the periphery of AMLs, which they did not observe in their case series. They further noted the presence of epithelial cysts located completely outside the kidney, which is incompatible with entrapment of native renal parenchyma.<sup>2</sup> On the basis of these observations, Mikami et al.,<sup>9</sup> speculated that the epithelial cysts may represent a component of the neoplastic process. In support of this, Filho et al.,<sup>15</sup> demonstrated expression of melanocytic markers in the epithelial lining of the cysts, suggesting neoplastic differentiation from AML. However, this finding is documented only in a single case and has not been reproduced in other published reports. Several authors have acknowledged that either mechanism may be possible.<sup>7,10,16,17</sup> More recently, Li et al.,<sup>13</sup> made use of the immunohistochemical stains glycoprotein non-metastatic melanoma protein B (GPNMB) and tuberous sclerosis 2 (TSC2) to demonstrate aberrant expression in the stromal component of AMLEC cases, while a normal immunoprofile was observed in the epithelial cysts and adjacent renal parenchyma, suggesting that these cysts represent entrapped tubules. In the present case, positive expression for PAX8 and lack of expression for melanocytic markers of the epithelial lining is more in keeping with renal tubular derivation, though conclusions regarding cyst origin cannot be definitively drawn.

Due to its complex histomorphology, AMLEC may be confused with a variety of benign and malignant renal tumors. Renal cell carcinoma is the most commonly cited malignant mimic of AMLEC in published cases, both radiologically and histopathologically.<sup>3,7,10-13,18</sup> In particular, clear cell renal cell carcinoma with cystic architecture in which neoplastic cells line cystic spaces, may closely resemble AMLEC, which has also been shown to exhibit clear cell change within the epithelial lining.<sup>3-4,9</sup> In the present case, a renal cell carcinoma with a sarcomatoid component was also considered due to the presence of a prominent spindle cell stroma. Another malignant entity entertained in the differential diagnosis of this case is synovial sarcoma. Similar to AMLEC, biphasic synovial sarcoma is composed of both spindle cell and epithelial components, with the latter forming glandular spaces lined by cuboidal to columnar cells.<sup>19</sup> Among the benign

mimics, mixed epithelial and stromal tumor (MEST) is regarded as one of the prime differentials owing to its substantial morphologic overlaps with AMLEC.<sup>19</sup> Like AMLEC, MEST exhibits a biphasic architecture composed of epithelial cysts lined by cuboidal or hobnail-shaped cells embedded in a spindle cell stroma that also expresses ER, PR, and CD10.<sup>1</sup> By immunohistochemistry, positivity for HMB45 and Melan A in the subepithelial cambium-like layer and spindle cell component can reliably distinguish AMLEC from its benign and malignant mimics, which lack melanocytic expression.<sup>4</sup>

Recent case reports have identified alterations in TSC1 and TSC2 in sporadic cases of AMLEC. Song et al.,<sup>8</sup> reported a case with a TSC2 nonsense mutation, while Xu et al.,<sup>18</sup> described a fat-poor AMLEC harboring a TSC1 splice-site mutation. In addition to lending support to the discussion on the origin of epithelial cysts, GPNMB and TSC2 immunostains were utilized by Li et al.,<sup>13</sup> to demonstrate underlying TSC2 pathway alterations in a number of AMLEC cases.

AMLEC is considered a benign renal neoplasm, and to date, there have been no reported cases of recurrence, metastasis, or malignant transformation. Most patients described in the literature underwent surgery in the form of partial or radical nephrectomy, commonly because of preoperative radiologic suspicion for renal cell carcinoma.<sup>2-4</sup> When follow-up information is available, reported outcomes have been favorable, with patients remaining alive and without evidence of disease following resection.<sup>3,4,6-10,16-18</sup>

## CONCLUSION

Angiomyolipoma with epithelial cysts is a rare renal neoplasm with a limited number of reported cases in the literature. Owing to its tendency to mimic malignancy on imaging and its close morphologic overlap with several benign and malignant renal tumors, AMLEC should be considered in the differential diagnosis of solid to cystic renal neoplasms. Careful histopathologic evaluation, supplemented by immunohistochemistry, is essential for accurate diagnosis.

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## ETHICAL CONSIDERATIONS

All efforts to secure patient's consent have been exhausted. The patient's anonymity is ensured. No other identifiers were included.

## STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

## AUTHOR DISCLOSURE

The authors declared no conflict of interest.

## DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed for this study.

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None.

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