



## A Rare Highly Aggressive Tumor of the Kidney: The Pure Epithelioid Angiomyolipoma

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### Authors' contributions

This work was carried out in collaboration between all authors. Author IM managed the acquisition of the data. Author MAB performed the drafting and the analysis of the manuscript. Author SBR managed the conception and design. Author MN performed the immunohistochemical study. Author RK is the surgeon who performed the surgery. Author AB did critical revision of the manuscript. Author BL read and approved the final manuscript.

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Case Study

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### ABSTRACT

**Aims:** The authors presents a case of pure Renal epithelioid angiomyolipoma (EAML) and discuss the clinicopathological characteristics and the diagnosis problems of this entity.

**Case Presentation:** A 51 year-old man presented with a persistant pain in the left lumbar region. Imaging revealed a left kidney tumor that was hemorrhagic and necrotic on gross examination. At histology, proliferation of 99% of atypical epithelioid cells, staining for HMB-45 and Melan A was observed. Our patient had lung and right adrenal metastasis six months after surgery and succumbed one year later.

**Conclusion:** In summary, the pure form of EAML is extremely rare. When diagnosed, the risk of tumor progression is high, especially if other histological predictive parameters of progression are observed. In that case, active treatment should be undergone and patients should be closely monitored.

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**Keywords:** Epithelioid variant; renal angiomyolipoma; renal neoplasm; histology; immunohistochemistry.

## 1. INTRODUCTION

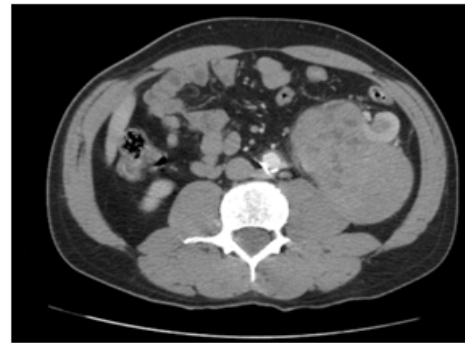
Renal epithelioid angiomyolipoma (EAML) has been recognized as a mesenchymal tumor in the 2004 World Health Organization classification of renal tumors [1], and a member of the family of PEComas [2], which may occur sporadically or in association with tuberous sclerosis complex (TSC). EAML is considered a potentially malignant neoplasm, since one third of the reported cases of EAML developed metastatic lesions [1]. The "pure" form of EAML is extremely rare. It is composed of predominant or pure epithelial component and has minimal to no adipocytic component [3]. We herein report a case of pure EAML of the kidney.

## 2. CASE REPORT

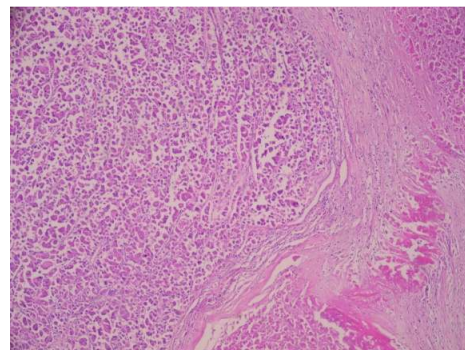
We herein report the case of a 51 year-old man presented with complaint of a persistent mild pain in the left lumbar region. He denied hematuria, abdominal pain or recent illness. He denied personal or family history of genitourinary disease. Past medical history was not significant. The patient denied previous abdominal or genitourinary surgeries. Vital signs were within normal limits. Physical exam could not find any palpable lumbar mass or tenderness. Urinalysis showed no blood, leukocytes, or protein. A renal ultrasound revealed a 12 cm hypoechoic mass within the upper pole of the left kidney. Serum laboratory tests were within normal limits, there was no polycythemia, neither hypercalcaemia. Computed tomography (CT) of chest, abdomen and pelvis with intravenous contrast showed soft tissue mass of heterogeneous density, which measured 12x10 cm and occupied the upper pole of the left kidney (Fig. 1). Scattered necrosis and calcification were occasionally observed, and the lesion exhibited moderate heterogeneous enhancement during enhanced scanning. Radiographically, the mass was considered to be renal cell carcinoma. No renal vein involvement was observed. It also showed an infiltration of the peri-renal fat and of the lombo-aortic nodes with no nodules in the liver, nor in the lung. The patient underwent a radical left nephrectomy with no complications. Gross pathology examination revealed a 11x10x8 cm whitish, non encapsulated mass with foci of necrosis and haemorrhage.

The mass invaded the renal sinus. The renal capsule was not invaded. No tumor thrombus in the renal vein was noted.

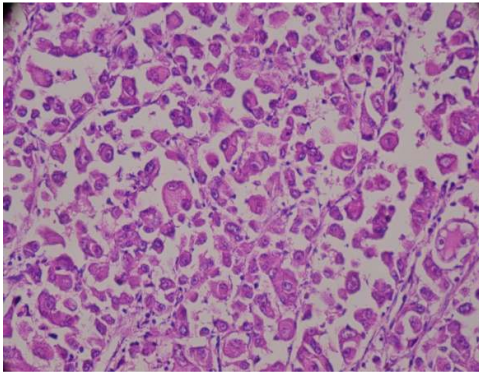
Routine Hematoxylin- and Eosin stained tissue sections revealed the mass to be composed of round pleomorphic and occasionally giant multinucleated tumor cells in a predominantly insular pattern (Fig. 2). Tumor cells had abundant eosinophilic cytoplasm, macronucleoli, and many atypical mitotic figures (Fig. 3). No adipous cells or smooth muscle cells were observed. Immunohistochemical stains were performed. The tumor cells showed strong uniform cytoplasmic reactivity for Melan A (Fig. 4). The cells also showed a strong and patchy positivity for HMB-45 and a negativity for epithelial markers (epithelial membrane antigen, pancytokeratin) and Myogenin.



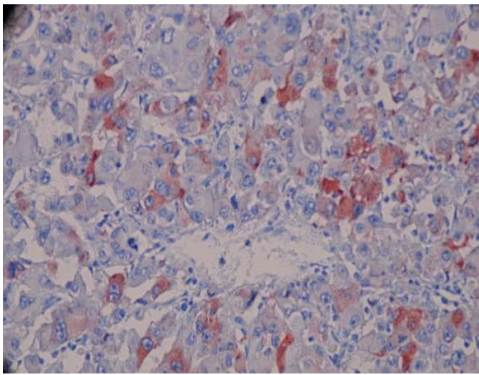
**Fig. 1. Axial images of computed tomography scan showing 10 cm left upper pole mass**



**Fig. 2. Hematoxylin-Eosin x100 staining showed polyedric epithelioid proliferation in a primarily insular pattern with a large zone of necrosis**



**Fig. 3. Hematoxylin-Eosin x400 the tumor cells have abundant eosinophilic cytoplasm, distinct cell borders, and macronucleoli with many atypical mitotic figures**



**Fig. 4. Melan A staining at 400 magnification showed strong cytoplasmic staining**

Given the histological findings, as well as the immunohistochemistry, the final diagnosis was pure epithelioid angiomyolipoma of the kidney.

Postoperative CT imaging conducted at six months of follow-up identified lung and left adrenal metastasis. In consequence, the patient was subjected to oral Mammalian target of rapamycin (mTOR) inhibitor. It was given 10 mg daily without an interruption. The patient succumbed to neoplastic progression of the disease twelve months later.

### 3. DISCUSSION

The epithelioid variant of renal angiomyolipoma is a rare entity. Its pure form, predominantly composed of epithelioid cells, is extremely rare. It occurs in 1 % of renal AML [4]. Its occurrence in association with TSC is higher than classic angiomyolipoma [1].

Clinically, patients are frequently symptomatic, presenting with lumbar pain; some tumors are discovered during tuberous sclerosis follow-up. Our patient had no history of TS and presented with a left lumbar pain. Imaging studies closely mimic renal cell carcinoma due to the low abundance of adipocytes in this tumor [1].

Histologically classic angiomyolipoma has three components: mature adipose tissue, dysmorphic blood vessels, and spindle-shaped smooth muscle cells. In EAML, epithelioid cells are polygonal, atypical, with abundant cytoplasm, vesicular nuclei and prominent nucleoli. Some authors have suggested that at least 5% of cells must exhibit epithelioid histology to set the diagnosis of EAML [5]. In our case, the tumor was totally composed of epithelioid cells.

Like in our case, EAML is usually positive for HMB45. However, Samantha E. Hohensee et al published the first case of Epithelioid angiomyolipoma of the kidney in a 50-year old man with no history of tuberous sclerosis, and with a tumor marker profile negative for HMB45 and Melan-A, although electron microscopic examination of tumor cells confirmed the presence of premelanosome-like granules [6].

Martignoni et al. [7] first reported fatal cases of EAML in 1994. In fact EAML metastases in one third of the cases. The liver and the lung are the most common sites of metastasis. Tumors with necrosis, mitotic activity, nuclear anaplasia, and external spread should raise significant concern for malignant outcome [1].

However, there are no histological criteria for malignant EAML, with the exception of distant metastases, which are accepted to be a definite sign of malignancy. Many recent studies examined histological parameters predictive of malignant behavior. Thus, Brimo et al suggested that the presence of at least three of four specific histological findings could predict malignant behavior of EAML. These histological findings are: cellular atypia in  $\geq 70\%$  of the epithelioid cell population; mitotic count greater than 2/10 HPF; presence of atypical mitotic figures; and necrosis [8]. Jun Lei et al. (9) compared histological criteria in progressor and no progressor patients. A high percentage of epithelioid cells, marked atypia and large mass diameter were predictive of tumor progression. Nese et al. [10] studied 41 cases of pure EAML. Recurrence and metastasis were seen in 17% and 49% of patients; 33% of patients died of the disease. The 5 adverse

prognostic parameters of Pure EAML were: tuberous sclerosis complex or concurrent angiomyolipoma, necrosis, tumor size >7 cm, extra-renal extension and/or renal vein involvement and carcinoma-like growth pattern. Recent studies also suggested that Ki67 index exceeding 10% and P53 overexpression and mutations in EAML may indicate the malignant behavior of the tumor [11].

In our case, necrosis, high mitosis index, marked atypia, vascular involvement, and predominant epithelioid cells component were predictive of tumor progression. In fact, our patient had lung metastasis six months after surgery and died of tumor progression one year later. With clinical, imaging, gross examination, histological parameters and the presence or not of extra-renal extension, a prognostic classification of EAML into benign, potentially malignant, and malignant is possible. The former two are treated as classic AML. Malignant EAMLs are treated as a clear cell carcinoma [12].

#### 4. CONCLUSION

EAMLs may occur sporadically or as part of TSC. Clinical symptoms and radiological findings are similar to those found in renal cell carcinoma. Nevertheless, preoperative diagnosis is difficult and requires pathological confirmation. They can be locally aggressive and metastatic as in our case. Due to its rarity and the lack of data regarding its management, it is essential to initiate appropriate treatment with close follow-up.

#### CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this paper and accompanying images'.

#### ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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