Epitheloid Angiomyolipomas of the Kidney: Rare Renal Tumors Associated With Poor Prognoses

Julian Aquilina, Joana B. Neves, Soha El-Sheikh, My-Anh Tran-Dang, Miles Walkden, Ravi Barod, Prasad Patki, Faiz Mumtaz, Axel Bex, and Maxine G.B. Tran

OBJECTIVE
To demonstrate the clinical spectrum and challenges associated with clinical management of epitheloid angiomyolipomas (eAML).

METHODS
We retrospectively reviewed the surgical database of a high-volume tertiary kidney cancer center from 2015 to 2020 to identify cases with a final histological diagnosis of eAML. Descriptive analysis of all cases was conducted.

RESULTS
Five surgical cases of eAMLs were identified. Two of which have had no tumor recurrence since surgery, and three patients passed away due to disease progression.

CONCLUSION
eAML are rare renal tumors which the World Health Organisation (5th Edition, 2022) and International Classification of Diseases for Oncology classify as having unspecified, borderline, or uncertain behavior. Here, we report that can also demonstrate aggressive behavior with fatal consequences. Post-operative follow-up should be recommended for all, with shorter intervals for patients with poor prognostic factors.

Epidemiology
Epitheloid angiomyolipomas (eAMLs) have been described as a rare variant of renal angiomyolipomas and are recognized as a distinct entity by the World Health Organization Classification of Tumours.1 eAMLs are classified as having unspecified, borderline, or uncertain behavior, but often display malignant behavior in up to one-third of cases, with the most common sites of metastasis being the liver, lung and regional lymph nodes.2 There is a preponderance in females (4:1), with a mean age around 54 years.3 EAMLs are mostly sporadic, but can also be associated with the tuberous sclerosis syndrome in up to a quarter of cases.4 We present a case series of five patients diagnosed with EAMLs that illustrate the spectrum of disease and the challenges with clinical management.

METHODS
We performed a retrospective review of the surgical histology database of a high-volume UK tertiary kidney cancer center from 2015 to 2020. Inclusion criteria included patients with a final histological diagnosis of epitheloid AML, as defined by the 2022 World Health Organisation Classification of Tumours.1 Histologically, eAMLs can be distinguished from classical AMLs by the predominance (> 80%) of epitheloid cells, low-fat cell content and cytological atypia. Immunohistochemistry reveals positivity for Melan A, SMA (smooth muscle actin) and melanocytic markers such as HMB-45 and HMB-50. Poor prognostic features of EAMLs include the presence of coagulative necrosis, perinephric fat invasion, renal vein invasion, atypical mitosis, maximum diameter over 7 cm, and confirmed Tuberous Sclerosis.1-7 Descriptive analysis of all cases was conducted.

RESULTS
Case 1
A 62-year-old female with normal renal function presented incidentally with a 33 mm completely endophytic mass in the right kidney. No intralesional fat was present on imaging. There was no personal or family history of tuberous sclerosis. Laparoscopic radical nephrectomy was performed, with a final diagnosis of EAML without poor
prognostic features. Three years post-nephrectomy, no recurrence was found.

**Case 2**
A 54-year-old female presented with worsening left lower quadrant abdominal pain, over the previous months. She had no family history of tuberous sclerosis syndrome. Cross-sectional imaging incidentally showed a left sided 34 mm renal mass. No intralavosal fat was present on imaging. All management options were discussed with the patient, including active surveillance, percutaneous biopsy or to proceed with surgery. The patient requested a biopsy, which revealed a core of tissue infiltrated by epithelioid cells, scattered giant cells and significant nuclear pleomorphism. Immunohistochemistry revealed a positive result for Vimentin, but negative staining for CK7 (cytokeratin 7), CK20 (cytokeratin 20), renal cell carcinoma (RCC) and CD117 (Cluster of Differentiation protein 117). A provisional diagnosis of a high-grade renal-cell carcinoma was made. Laparoscopic radical nephrectomy was performed and on analysis of the surgical specimen, a final diagnosis of EAML without poor prognostic features was reached. Follow-up six months post-nephrectomy, there was no evidence of tumor recurrence.

**Case 3**
A 48-year-old female with known tuberous sclerosis presented asymptomatically. She had reduced renal function (estimated glomerular filtration rate of 40 mL/min/1.73 m²) and family history of a brother, also affected by tuberous sclerosis, who died of metastatic EAML. CT (computerised tomography) scan revealed multiple bilateral AMLs and a 5.4 cm lesion in the lower pole of the left kidney with a more solid consistency. Biopsy of this lesion confirmed EAML with poor prognostic features of atypical mitosis and lymphovascular invasion. The patient declined surgery and opted to postpone definitive treatment. Eight months after diagnosis she was admitted to hospital after an acute bleed from the right-sided AML. At this time, she was diagnosed with metastatic disease with enlarged left-sided perirenal lymph nodes and multiple pulmonary nodules. Treatment with Sirolimus was started and changed to Sunitinib 6 months later due to disease progression. In the intervening period, there had been multiple hospital admissions for acute bleeding from the AMLs and hemodialysis was commenced. One month after starting sunitinib, the patient was admitted to hospital with acute bleeding arising from the left-sided tumor. An urgent open radical nephrectomy was performed for hemostasis, which was complicated with sigmoid colon perforation and need for colostomy. At 18 months after the initial diagnosis, the patient died due to disease progression.

**Case 4**
A 43-year-old previously fit male presented with intermittent abdominal discomfort for the previous two years. He had no personal or family history of kidney cancer or tuberous sclerosis. On examination, a palpable abdominal mass was felt. On cross-sectional imaging, a large tumor was found in the right kidney, measuring 240 mm in the largest axis. A right open radical nephrectomy was performed and a diagnosis of EAML was histologically confirmed after analysis of the surgical specimen. Microscopic analysis revealed poor prognostic features such as atypical mitosis, coagulative necrosis, hilar, perininephric adipose tissue, and renal vein invasion. Regional lymphadenectomy was negative for metastasis. One year after surgery, local recurrence in the right nephrectomy bed was documented. The patient started systemic therapy with Sunitinib, however suffered from disease progression and died 2 years after diagnosis.

**Case 5**
A 59-year-old male with a known diagnosis of tuberous sclerosis had been on annual MRI (magnetic resonance imaging) surveillance for 10 years following embolization for a 6 cm right-sided classic AML. Imaging revealed that a lesion that had previously the appearance of a classical AML and measured 3.3 cm in maximal diameter the previous year, had enlarged to 8.5 × 7.8 cm (as shown in Fig. 1). A right-sided laparoscopic radical nephrectomy and regional lymphadenectomy were performed. Surgical pathology confirmed the diagnosis of EAML. The tumor had metastasized to three regional lymph nodes and exhibited poor prognostic features such as atypical mitotic figures, coagulative necrosis, vascular invasion, and tumor thrombi in many vascular channels. The first post-operative MRI scan performed at 6 months showed no recurrence; however, the patient was admitted with hypercalcemia a further 3 months later. An MRI at this time showed extensive recurrent disease, with the largest measuring 192 mm × 99 mm × 118 mm in the right flank with extensive ill-defined soft tissue extending towards the liver, lesser sac and a 70 mm × 70 mm mass in the recto-vesical pouch. The patient was started on Everolimus but suffered from disease progression and died 18 months post nephrectomy (Fig. 2).

**DISCUSSION**
The epithelioid variant of angiomylipoma belongs to the perivascular epithelioid cell family of tumors. EAMLs are rare renal tumors which although are classified as benign, can frequently display malignant behavior, with poor patient outcomes despite surgical excision.

EAML can only be definitively distinguished from benign AML by microscopic phenotypic analysis. Histologically, they display low fat-cell content, presence of epithelioid cells in more than 80% of the tumor, and cytologic atypia. Typical morphology can resemble high-grade RCC with sarcomatoid differentiation, as seen in case 2. Both EAMLs and classical AMLs can exhibit positivity for HMB-45 and Melan-A expression, vimentin, desmin and other smooth muscle cell markers, so immunohistochemistry cannot be used to reliably distinguish between the two.

Currently no clinical practice guidelines exist specifically for the management of EAML. Given the potential
Figure 1. Renal MRI images from the patient described in case 5. (A) Image taken 1 year prior to surgery, depicting multiple lesions with features suggestive of classical angiomyolipomas. (B) Image taken just before surgery depicting a large heterogeneous enhancing lesion measuring 8.5 × 7.8 cm arising from the posterior upper pole of the right kidney, previously measured 3.3 cm indicative of fast interval growth. (C) An MRI 6 month post operatively shows no evidence of recurrent disease, however just 3 months later the patient had an MRI during hospital admission with hypercalcemia and was found to have extensive recurrent disease (D).

Figure 2. Microscopic images of the epitheloid AML from the patient described in case 5. (A) Primary tumor, H&E staining (B) Lymph node metastasis, H&E staining, 50×. Immunohistochemistry shows that the tumor is positive for Melan A (C) and SMA (D), both 200×.
malignant behavior of these tumors, as seen for cases 3, 4 and 5, surgical excision is often recommended. A change in imaging characteristics or growth kinetics in previously classical AMLs should alert clinical suspicion of underlying EAML pathology and trigger active treatment discussions with the patient, as illustrated by cases 3 and 5.

Although these renal tumors are rare, there have been some studies that explore the outcomes of patients with EAMLs. The clinical implications of EAML have been mixed. Faraji et al. reviewed 40 case reports and series of EAML, totaling 69 cases. Adverse outcomes (metastasis or death due to disease) were found in 40% of patients (follow-up, 22.5 ± 18 months). Nese et al. analyzed 41 cases of kidney EAML, and found a 17% rate of recurrence and 49% metastasis rate, with 33% of patients dying of EAML. Of our 5 cases presented, 3 died from disease progression, which further highlights the difficulty in counseling and managing patients with these ‘benign’ tumors.

There are currently no specific guidelines on systemic treatment for metastatic EAML either. The lack of studies dedicated to EAML management means that uncertainty persists regarding the most appropriate systemic treatment to offer these patients. The development of a new form of immune modulation via checkpoint inhibition, has changed the management of metastatic RCC, and these drugs are now considered first-line treatment for intermediate and high-risk cases. However, no phase III trials have been reported for metastatic kidney tumors that are not RCC. This again exposes the difficulties in managing rarer metastatic kidney tumors such as EAML. A multicentre observational retrospective study compared oncological outcomes of four systemic therapy regimens (anthracycline-based, gemcitabine-based, VEGF inhibitor and Mammalian target of rapamycin inhibitors) in 53 patients with locally advanced or metastatic perivascular epithelioid cell tumors, eleven of these patients had EAML. Mammalian target of rapamycin inhibition was found to have the greatest response rate and progression-free survival in advanced/metastatic perivascular epithelioid cell tumors (76.9% and 9 months, respectively). A double-blinded randomized controlled trial by Bissler et al. reported that patients with angiomyolipoma responded well to Everolimus, demonstrating continuous angiomyolipoma shrinkage with no hemorrhages over a median treatment time of 28.9 months. However, more studies are needed to fully evaluate its long-term effects, particularly in the epitheloid variant of angiomyolipoma.

CONCLUSION

EAMLs are rare renal tumors which although classified as benign, can straddle the two sides of tumor behavior. The risk of tumor progression is significant and a high index of caution should be taken, particularly if poor prognostic features are observed. While no specific guidelines on the management of EAMLs are currently available, existing evidence supports surgical excision and postoperative monitoring tailored to individual patient and tumor characteristics. Further research and clinical trials are required to address the unmet clinical need to improve understanding and outcomes in patients diagnosed with EAML.

References