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Review

Renal Epithelioid Angiomyolipomas: Clinicopathological Features, Diagnosis, and Management

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Abstract

Renal angiomyolipomas (AMLs) are typically benign, fat-rich mesenchymal tumours composed of vascular, smooth muscle, and adipose elements. However, rare fat-poor subtypes, particularly epithelioid angiomyolipoma (EAML), pose significant diagnostic and therapeutic challenges due to their malignant potential and morphological overlap with renal cell carcinoma (RCC). EAML represents less than 1% of AMLs but differs markedly in its biological behaviour, with a propensity for local invasion, lymphadenopathy, and distant metastasis, most commonly to the lungs and liver. Preoperative diagnosis is often delayed or incorrect, as imaging may fail to detect fat-deficient lesions, making histopathological evaluation necessary. EAML is defined by sheets of polygonal epithelioid cells with eosinophilic or clear cytoplasm, prominent nucleoli, and frequent mitotic figures. Genetic alterations in TSC1/TSC2 and activation of the mTOR pathway are central to pathogenesis, particularly in tuberous sclerosis complex-associated cases. Management hinges on surgical resection, yet recurrence and metastasis may occur years after nephrectomy. mTOR inhibitors have demonstrated efficacy in tumour reduction, especially in TSC-linked cases, while VEGF pathway inhibitors and immune checkpoint blockade represent promising but underexplored avenues. Prognostic features include tumour size >9 cm, necrosis, vascular invasion, and high epithelioid cell proportion. Given the rarity and aggressive potential of EAML, long-term surveillance and multidisciplinary care are essential. Continued research into molecular drivers and targeted therapies will be critical to improving diagnostic precision and patient outcomes.

Keywords: Angiomyolipoma, renal cell carcinoma, tyrosine kinase inhibitors, immunotherapy, targeted therapy, review.

Introduction

Renal angiomyolipomas (AMLs) are benign neoplasms of the kidney typically composed of a triphasic morphology of vascular, smooth muscle, and adipose tissue, though rare atypical types may be of monophasic or epithelioid histology (1, 2). Once considered hamartomas and choristomas, AMLs

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are currently classified amongst the family of perivascular epithelioid cell tumours (PEComa) (3-5).

AMLs are the most common benign renal tumours associated with an overall prevalence of 0.44% and a strong predisposition to females who represent twice as many cases compared to males (0.60% females *versus* 0.28% males) (6). A more recent retrospective surgical cohort (2001-2021) found that 70.5% of AML cases were women (female-to-male ratio ≈ 1:2.4); 42% were diagnosed incidentally (7). Sporadic cases comprise 80% of AMLs, while 20% may present as part of tuberous sclerosis (TSC) or rarely pulmonary lymphangioleiomyomatosis (LAM), a condition observed almost exclusively in women (4, 8, 9).

Different types of renal AMLs exist forming a heterogeneous group of neoplasms which display different pathological, radiological, and clinical features (10). Imaging is crucial in the diagnosis and management of renal AMLs with the detection of adipose tissue constituting an essential diagnostic criterion (8). However, despite having a classic triphasic morphology, certain AMLs display poor fat content on macroscopic imaging, thus rendering it difficult to preoperatively distinguish them from renal cell carcinoma (RCC) to prevent unnecessary nephrectomy for a benign tumour (5, 11-16).

AML with epithelial cysts (AMLEC) is an extremely rare subtype of benign, fat-poor AML that was only classified in 2017 (10) following the publication of two case series in the literature (17, 18). In contrast, epithelioid AML (EAML) is a rare distinct variant (1%) of fat poor AML of mesenchymal origin, which may undergo malignant transformation (19, 20). EAML is characterised by p53 mutations (21) and local aggressiveness, including lymphadenopathy and distal metastases to the lung, liver, mediastinum, and vertebrae (22, 23) in a third of cases (9, 21, 24-26). Size correlates to risk of spread (10, 27) and over half of EAMLs are associated with TSC (28). This malignant phenotype contradicts that of typical AML, which has historically proven benign in hundreds of cases, except for two reports, in which high-grade leiomyosarcoma arose from typical angiomyolipoma (29, 30).

Diagnosis

EAML poses a diagnostic challenge given its clinico-pathological resemblance and similar epithelioid morphology to RCC (31), sarcoma, and medullary carcinoma (32, 33). Additionally, EAML may coexist simultaneously with clear cell RCC (33, 34). Therefore, diagnosis often depends on postoperative histopathological assessment (35).

Histologically, EAML is characterised by predominant proliferation of atypical, polymorphic, round to polygonal epithelioid cells featuring abundant clear or densely stained eosinophilic cytoplasm, enlarged vesicular nuclei and often prominent nucleoli similarly to ganglion cells. Short spindle cells and multinucleated giant cells may also be present (32). Some authors suggest a requirement of at least 5% (36) or 10% (37) epithelioid histology for the diagnosis of EAML, though >80% is often quoted as an appropriate cut-off for malignant transformation (38, 39), while others report nearly pure epithelioid composition (40, 41).

Immunohistochemical staining for human melanoma black (HMB)-45-positive epithelioid cells, in the absence of adipocytes or minimal adult-appearing fat tissue, serves as a useful marker for EAML diagnosis (42). Moreover, CD-68 positivity and cytokeratin negativity are paramount in aiding EAML identification. Positive immunostaining for Melan-A, muscle-specific actin and, rarely, smooth muscle actin may also be featured with negative reactivity against epithelial membrane antigen (32).

Treatment

Malignant AML is always managed by partial or radical nephrectomy followed by adjuvant chemotherapy (2, 43). Surgical decision-making is guided by the diagnosis and radiology-derived nephrometric scoring when partial nephrectomy is planned (43). Recently, an increasing number of AMLs are managed with selective arterial embolization and percutaneous ablation, which are associated with less morbidity compared to traditional surgery (43) Integrated approaches, including surgery,

chemotherapy, and molecular-targeted therapy, should be considered upon EAML diagnosis. Follow-up is indicated in EAMLs with necrosis, >9 cm tumour size, venous thrombosis, >70% epithelioid cells or >60% cellular atypia (35). Surgery remains the most effective approach for EAML, although still often insufficient. Recurrence or distant metastasis occur within 1.5-9 years postoperatively (23, 28, 44-48).

Chemotherapy and targeted therapy. Since EAML is a PEComa, which has similar histological features with to lymphagioleiomyomas and clear cell "sugar" tumours of the lung and pancreas (3), it may respond to chemotherapies such as doxorubicin, cyclophosphamide, and cisplatin on long-term follow-up (25, 49).

Furthermore, mTOR inhibitors rapamycin/sirolimus (50), everolimus (51), and temsirolimus can achieve tumour regression and reduce gross tumour burden in patients with TSC-associated (52-58) and sporadic renal AMLs (59). A single institution retrospective study on advanced PEComas, including epithelioid variants, demonstrated that mTOR inhibitors offered similar survival and PFS outcomes compared to chemotherapy, but with potentially less morbidity, suggesting preferential use (60). Moreover, one study of 15 PEComa cases showed that the mTOR cascade was always activated, further supporting the use of mTOR inhibitors (61). This can be explained since TSC1/TSC2 genes are disrupted in patients with TSC and sporadic AML (62), thus encoding an abnormal TSC1/TSC2 protein complex that inappropriately regulates mTOR complex 1 (mTORC1) (Figure 1) (63). Dysregulated cell growth and increased VEGF expression occur from mTORC1-dependent HIF activation (64, 65). Indeed, a multicentre phase 2 trial showed that sirolimus was successful in inducing renal AML regression and decreasing baseline elevated serum VEGF-D which was shown to correlate to AML size (Spearman correlation coefficient 0.54, p=0.001, at baseline) (66).

Moreover, although the multi-kinase inhibitor sorafenib, prescribed as first/second line treatment for advanced and/or metastatic RCC, was ineffective in treating EAML according to one case report (67), sunitinib, a multi-kinase inhibitor used as second line treatment, was effective in achieving tumour regression according to a paediatric EAML case report (68). The same case report also showed that axitinib, an active selective inhibitor of VEGFR 1, 2 and 3, may offer therapeutic benefit. Specifically, when administered as third-line treatment, it effectively halted primary tumour growth postoperatively, although thoracic metastasis was observed in later disease stage. Subsequently, a phase 3 trial comparing pembrolizumab plus axitinib *versus* sunitinib for advanced RCC has proven that the former is superior in achieving significantly longer overall survival, progression-free survival, and a higher objective response rate (52). Further research is needed to determine the effectiveness of pembrolizumab plus axitinib in the treatment of renal AML. The advantage of axitinib and other single-target growth factor receptor inhibitors over multikinase inhibitors is that they have the potential to decrease toxicity while precisely targeting the VHL pathway in clear cell kidney cancer (69).

Prognosis and Future Directions

The prognosis of EAML remains guarded due to its potential for local recurrence and distant metastasis. Histological predictors of poor prognosis include marked nuclear atypia, necrosis, high mitotic rate (>1/50 high power fields), vascular invasion, and the presence of >70% epithelioid components or >60% atypical epithelioid cells. Clinical features such as tumour size >9 cm, involvement of renal vein or inferior vena cava, and non-resectability are also associated with a more aggressive clinical course.

Despite aggressive surgical management, the recurrence rate of EAML is non-negligible, with distant metastases most commonly affecting the lungs, liver, and bones. Metastatic progression may occur several years after primary tumour resection, highlighting the need for long-term surveillance. Advanced EAML is notoriously chemoresistant and lacks a standardized systemic

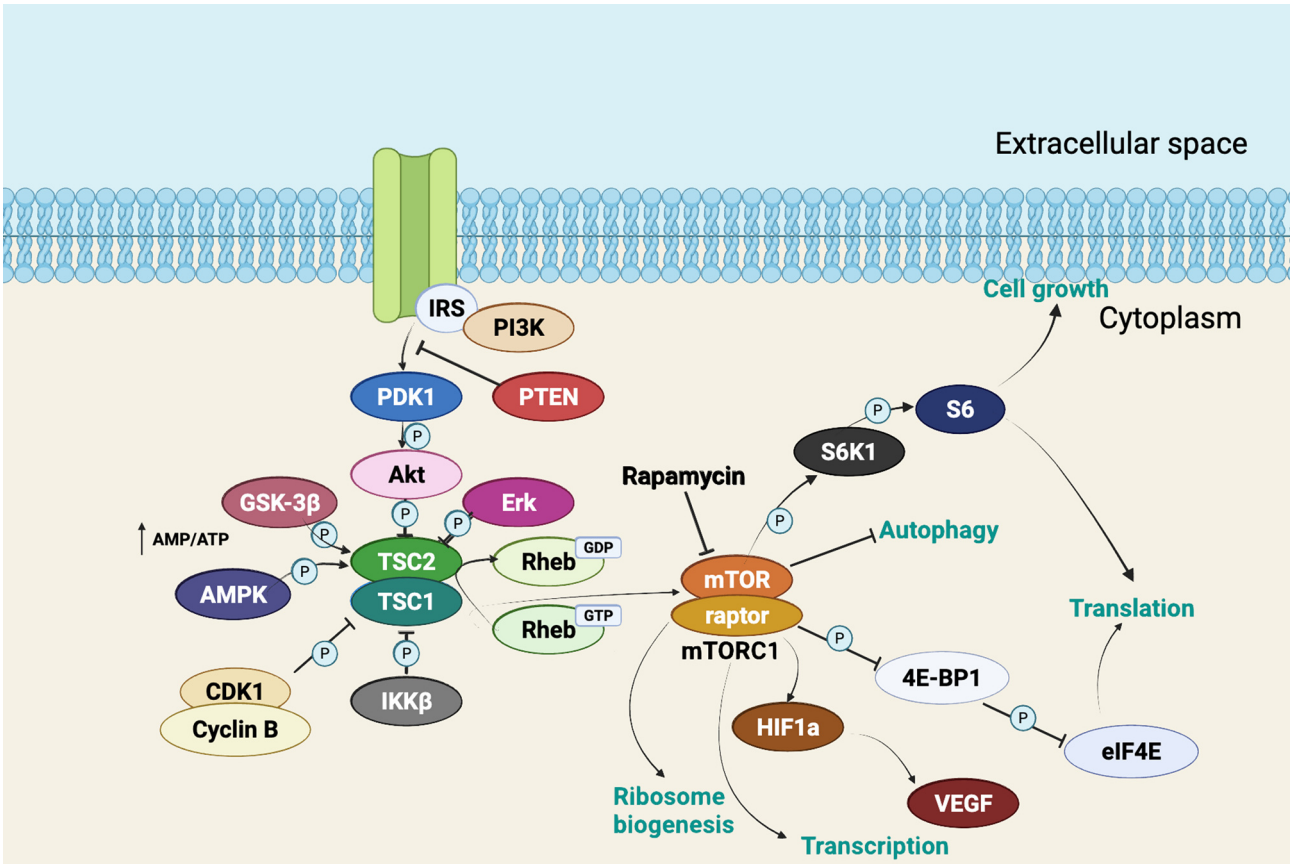

Figure 1. *The mammalian target of rapamycin (mTOR) pathway showing the role of tuberous sclerosis complex 1 (TSC1; hamartin) and TSC2 (tuberin) proteins. mTORC1, Mammalian target of rapamycin complex 1; VEGF, vascular endothelial growth factor receptor. Adapted from (63).*

treatment protocol, emphasizing the need for further research into novel therapeutic agents.

Recent genomic and transcriptomic analyses suggest that EAML and other PEComas may benefit from precision oncology approaches, especially with the identification of TSC1/TSC2 mutations and mTOR pathway activation as common oncogenic drivers (61, 62). mTOR inhibitors have shown considerable promise in both sporadic and TSC-associated cases; however, not all patients respond, possibly due to molecular heterogeneity and downstream resistance mechanisms.

The potential utility of immune checkpoint inhibitors (ICIs), such as pembrolizumab, remains under investigation. Genomic profiling of 34 malignant renal EAMLs revealed molecular features including microsatellite instability (MSI), tumor mutational burden (TMB), and PD-L1 expression, as well as potential targets for precision therapy (70). Given the immunogenic potential of EAML and its occasional expression of PD-L1, further studies are warranted to assess the efficacy of ICIs alone or in combination with VEGF/VEGFR-targeting agents like axitinib (64, 68, 69). Clinical trials specifically targeting malignant PEComas – including EAML – are crucial to refine these therapeutic strategies. Moreover, liquid biopsy and circulating tumour DNA (ctDNA) may offer valuable, non-invasive tools for monitoring disease activity, particularly in assessing residual disease and detecting early recurrence.

Conclusion

Renal AMLs represent a spectrum of mesenchymal neoplasms, with EAML forming a rare but potentially malignant variant. Although most AMLs are benign and easily diagnosable through imaging, fat-poor subtypes, especially EAML, can mimic RCC and necessitate histopathological evaluation for accurate diagnosis.

Management of EAML is complex, often requiring surgical intervention and adjunctive systemic therapy. Emerging treatments, particularly mTOR inhibitors and VEGF/VEGFR-directed therapies, have improved outcomes in selected cases. However, recurrent and metastatic EAMLs remain challenging to treat, underscoring the importance of molecular diagnostics, multidisciplinary care, and clinical trial participation.

Further research is required to refine diagnostic criteria, identify molecular biomarkers of aggression, and optimize targeted and immunotherapeutic regimens tailored to the unique biology of EAML.

Conflicts of Interest

The Author has no conflicts of interest to declare.

Authors' Contributions

KSR: Conceptualization, Drafting, Reviewing.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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