Review

A Review of Angiomyolipoma and Its Morphological Variants

Simpal Gill, MD, Edit Weber-Shrikant, MD, Frank Chen, MD, PhD

Abstract

Angiomyolipoma (AML) is defined as a benign clonal neoplasm composed of thick-walled blood vessels, smooth muscle cells and adipose tissue, belonging to the family of perivascular epithelioid cell tumors (PEComa). Morphologic variants of AML are composed of variable proportions of mature adipose tissue, thick-walled, poorly organized blood vessels, smooth muscle with or without feature of atypia and/or pleomorphism. Similar to all PEComas, AML demonstrates co-expression of melanocytic and smooth muscle markers, but negative for cytokeratin. This paper explores AML and its variants with the goal of distinguishing between these morphologic variants, and differentiating them from other renal malignancies.

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Key Words*: Kidney, angiomyolipoma, oncocytoma, clear cell renal cell carcinoma, epithelioid angiomyolipoma, tuberous sclerosis.*

Introduction

Angiomyolipoma (AML) is the most common benign mesenchymal neoplasm of the kidney, composed of a variable proportion of adipose tissue, spindled and epithelioid smooth muscle cells and abnormally thick walled blood vessels.[1] The triphasic nature of AML has led many in the past to consider these lesions as hamartomas, however, current clonality studies support their classification as neoplasms.[2] A growing body of literature has shown that AML demonstrates perivascular epithelioid cell (PEC) differentiation,[3,4.5] and belongs to the PEComa tumor family, which also includes lymphangiomyomatosis, clear cell "sugar" tumor of the lung, and a group of rare, morphologically and immunohistochemically identical tumors found at other locations.[3] The majorities of AMLs are sporadic and only occasionally are part of inherited tuberous sclerosis complex (TSC). TSC is a multiorgan disease, where renal involvement may progress insidiously and can be a significant cause of morbidity, and possible mortality, from retroperitoneal hemorrhage and renal insufficiency.[6-10] Most frequent renal findings in TSC patients are multiple AMLs, cysts, oncocytomas and carcinomas.[10] Classic AML has a triphasic histological appearance and contains all 3 of its namesake components. Occasionally, morphologic variants, such as oncocytic [11,12] cystic [13-15] and epithelioid [16-21] are seen. In the following, the classic AML and its morphologic variants will be described individually in succession.

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Classic AML

The classic AML (cAML) has three elements: mature adipocytes, irregular thick-walled blood vessels, and smooth muscle (**Figure 1A**). The gross appearance is distinctive and consists of soft yellow regions admixed with firm tan areas.[22] The color and consistency are variable and reflect the relative contribution of each component imparting uniqueness to each variant of the neoplasm. Of the three components, smooth muscle accounts for the greatest variability.[23] The interface between AML and the uninvolved kidney is typically distinct, although renal tubules may be seen entrapped at the periphery of some tumors on microscopic examination. The smooth muscle cells appear to spread out radially from blood vessels followed by a fascicular expansile growth thereafter (**Figure 1B**). Rarely, striking degrees of nuclear atypia with occasional mitotic activity and multinucleation may be noted in these cells, raising the possibility of a malignant process.[1]

Angiomyolipomas have a classic immunohistochemical staining profile, which often assists in making the diagnosis. The smooth muscle (spindled and epithelioid) component stains positive with mesenchymal markers such as vimentin, smooth muscle actin, muscle specific actin and melanocytic markers like HMB-45 (**Figure 1C**). Recent literature demonstrates positive staining of AML with CD 117 (c-kit). Epithelial markers are consistently negative in classic AMLs.[23]

A conservative approach is used to treat these tumors because the majority of renal AMLs are clinically benign and a malignant outcome is rare.[23]

AML, Epithelioid Variant

Epithelioid AML (eAML) is a rare, phenotypically aggressive, potentially malignant mesenchymal neoplasm, and is characterized by proliferation of predominantly epithelioid cells (**Figure 2A**).[24] These cells are polygonal with clear to eosinophilic cytoplasm and round to oval nuclei and

variable degrees of nuclear atypia (**Figure 2B**). Most importantly, no abnormal vessels or fat cells are seen. Epithelioid AML with a prominent cytologic atypia is also referred to as atypical AML.[25] This variant can be erroneously diagnosed as sarcoma or renal cell carcinoma (RCC), especially when other components of AML are obscure and atypia predominates.[26,27] As reported in the literature and confirmed by Aydin et al,[28] some epithelioid cells may have uniform clear to eosinophilic cytoplasm also called "small cell type", which was seen in a third of their eAML cases. The epithelioid morphology and degree of cytological atypia often imposes diagnostic difficulty and can potentially contribute to the misdiagnosis of eAMLs as RCCs or metastatic melanomas.[29,30] Brimo et al[31] developed a predictive model of 4 atypical features that included: (1) >=70% atypical epithelioid cells, (2) >= 2 mitotic figures per 10 hpf, (3) atypical mitotic figures, and (4) necrosis; the presence of 3 or all of the features was highly predictive of malignant behavior. This model accurately categorized 78% of clinically malignant and 100% of the clinically benign epithelioid AMLs with atypia.

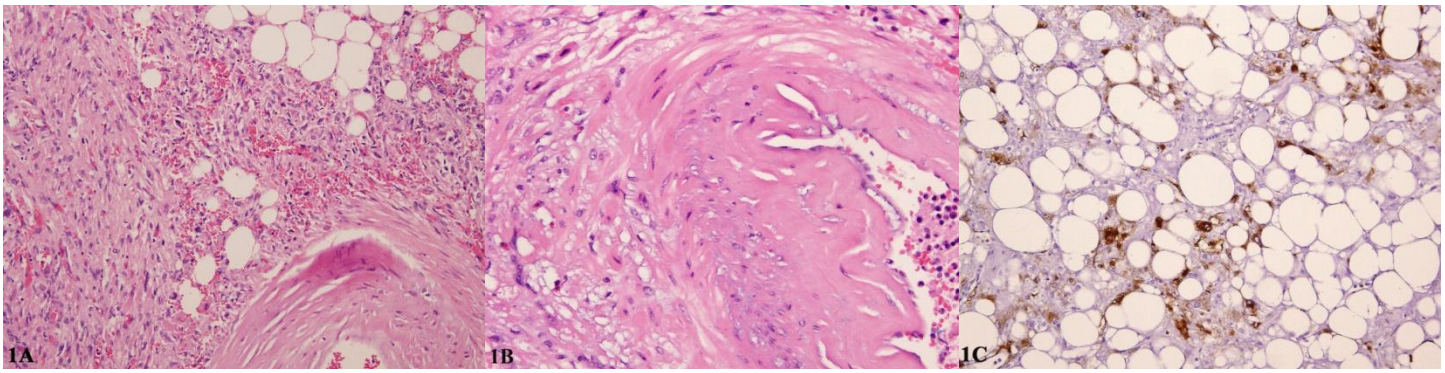

Figure 1. Morphological features of classic AML**. 1A**. Haphazardly arranged mature adipocytes, irregular blood vessels and smooth muscle (hematoxylin-eosin stain: original magnification x100). **1B**. The smooth muscle cells of blood vessels spread out in a fascicular expansile growth pattern (hematoxylin-eosin stain: original magnification x400). **1C.** The spindle cells scattered between the adipocytes stain positive with the melanocytic marker HMB-45 (hematoxylin-eosin stain: original magnification x100).

Positive immunostaining with HMB45 is very helpful for eAML identification (**Figure 2C**).[32] In a study by Stone et al,[33] a preferential positive staining of the epithelioid cells in eAML for the melanosome and melanoma markers HMB-45, HMB-50, NKI/C3, and tyrosinase was noted as compared to the spindled and adipocytic cells. The ultrastructural characteristics of the 3 cell types accounted for this preferential staining with the melanosome and melanoma markers. Qualitatively, the premelanosome-like crystalloid structures were more readily found in epithelioid cells. Cytogenetics can also be utilized to differentiate aggressive fat poor AML/eAML from the TFEB t(6;11) HMB45-positive pediatric RCC.[34] A differentiating feature using immunohistochemistry, is a diffuse staining with HMB 45 and Melan-A in eAML as compared to a focal staining in translocation RCC, which in addition lack the premelanosome-like structures as seen with the former.[35]

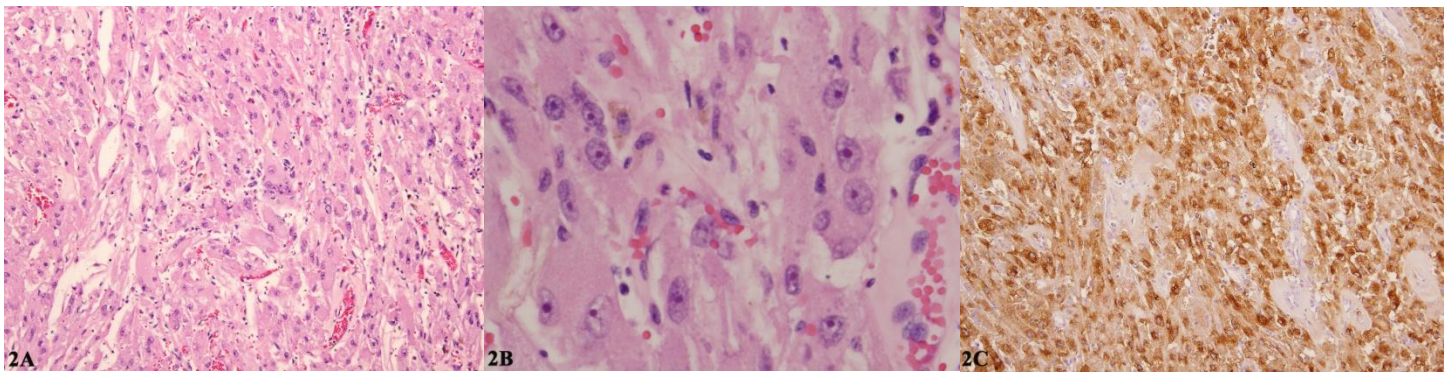

Figure 2. Morphological features of eAML. **2A.** eAML showing proliferation of predominantly epithelioid cells, which are polygonal with clear to eosinophilic cytoplasm**. (**hematoxylin-eosin stain: original magnification x100) **2B.** The epithelioid cells show variable degrees of cytologic atypia with few or no abnormal vessels or fat cells identifiable (hematoxylin-eosin stain: original magnification x400). **2C.** eAML shows diffuse positive immunostaining with HMB-45 **(**hematoxylin-eosin stain: original magnification x100).

AML oncocytoma – like variant

Rarely, AML can predominantly be composed of epithelioid cells exhibiting densely eosinophilic cytoplasm, reminiscent of oncocytoma. This has recently been described under the heading of real epithelioid oxyphillic neoplasm (REOM) or oncocytoma-like AML.[36] Recognition of oncocytoma-like angiomyolipoma is pertinent because oncocytomas have been reported to occur in the same kidney as AMLs. Moreover, in patients with tuberous sclerosis, co-existence of these two tumors is more frequent than that in the general population.[37] Immunohistochemistry can be very helpful in making the correct diagnosis, as oncocytoma-like AML tumors do not react with cytokeratins or epithelial membrane antigen, in contrast to the immunohistochemical phenotype typical of oncocytomas, described by Martignoni et al.[36]

AML, spindle cell – leiomyoma like variant

AML, spindle cell–leiomyoma like variant is referred to as "capsulomas" because it is often located in the subcapsular region of the kidney. It is composed almost entirely of smooth muscle cells (**Figure 3A** and **3B**). A pattern similar to lymphangioleiomyoma is exhibited by cells associated with thin walled, branching vessels and are another variation of the smooth muscle component.[1] This variant of AML is also positive for HMB-45 (**Figure 3C**). In the study by Stone et al,[33] muscle markers calponin and muscle-specific actin (HHF-35) preferentially stained the spindle-type cells. The staining pattern corresponded with the ultrastructural characteristics of the 3 cell types of AML. Qualitatively, the spindle-type cells contained more microfilaments than either the epithelioid cells or the adipocytes. The absence of S100 staining almost certainly excludes a myoepithelial origin of these cells. Furthermore, ultrastructurally, the lack of either Z-bands or Weibel-Palade bodies makes it unlikely that these cells originate from either skeletal muscle or endothelial cells.

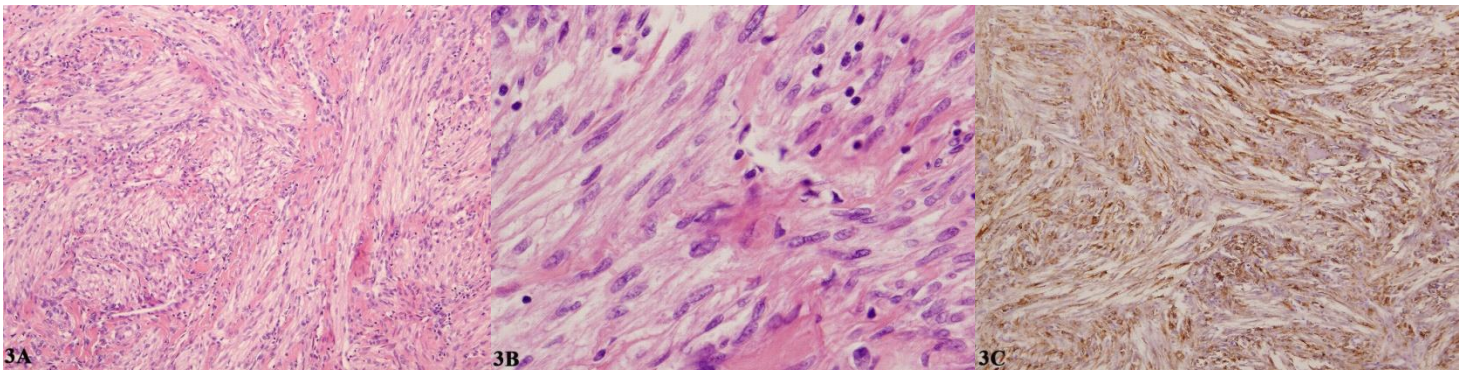

Figure 3. Morphological features of spindle cell- leiomyoma like variant of AML. **3A.** The tumor is composed almost entirely of smooth muscle cells **(**hematoxylin-eosin stain: original magnification x100). **3B.** High magnification shows the close resemblance to smooth muscle tumors like leiomyomas **(**hematoxylin-eosin stain: original magnification x400). **3C.** The spindle cell variant is positive for HMB-45 immunostain **(**hematoxylin-eosin stain: original magnification x400).

AML, liposarcoma – like variant

The lipomatous component of AML can give rise to a liposarcoma–like variant that typically consists of mature adipose tissue, but can have vacuolated adipocytes simulating lipoblasts. The presence of these "lipoblasts" raises the possibility of liposarcoma, especially when the adipocytic differentiation is extensive. The blood vessels show thick walls and are deficient in the normal elastic content of arteries.[1] Among the four cases described by Klapproth,[38] one had initially been erroneously diagnosed as liposarcoma, due to the absence of neither smooth-muscle tissue and thick-walled blood vessels on the sections examined. McCullough et al[39] examined seven cases, out of which the diagnosis of one was lipoma or liposarcoma on frozen sections. In light of such situations, extensive sampling of the tumor and HMB-45 stain are certainly helpful.

AML, vascular predominant variant

AML, vascular predominant variant shows a prominent vascular component which can mimic vascular malformations.[1] Karbowniczek et al[40] demonstrated five morphologically distinct vascular variations: cellular, collagenous, hemangiopericystic, glomeruloid and aneurysmatic types. They used laser capture microdissection to determine that four of the vessel types have TCS2 loss of heterozygosity (LOH) and are neoplastic. The fifth vessel type, collagenous vessels, did not have LOH, and is likely reactive. The LOH in all three components of AML (vessels, adipose tissue and smooth muscle), is in favor of the hypothesis that mesenchymal cells which have retained their differentiation plasticity give rise to AMLs. This differentiates AMLs from other benign vascular malignancies such as those in Von Hippel Lindau disease, in which the stromal cells are neoplastic and the vascular cells are not.

AML with epithelial cysts

Angiomyolipoma with epithelial cysts (AMLEC) is a rare cystic variant of angiomyolipoma.[1] These tumors can be confused with mixed epithelial-stromal tumor, however, the following features support them to be classified as AMLEC, including: the lack of female predominance or association with hormone therapy, the presence of characteristic

dysplastic blood vessels with a disorganized exterior muscular layer, and the immunohistochemical profile. Epithelial-induced müllerian differentiation can account for the peculiar subepithelial condensation of AML stromal cells with supportive morphologic and immunohistochemical features.[10] AMLEC can readily be distinguished from most adult cystic renal lesions. When confronted with a grossly cystic lesion, one must always exclude the possibility of cystic variants of RCC, in particular the multilocular cystic variant of RCC, which is characterized by multiple cystic spaces separated by delicate septa.[41,42] Similarly, the absence of calcifications, necrotic debris, cholesterol clefts and concomitant renal cell carcinoma or papillary carcinoma does not support the possibility of cystically necrotic RCC.[41]

Summary

Although diagnosis of AML is straightforward in the majority of cases, AML variants show predominance in one of the three components that may attribute to an erroneous diagnosis of malignancy and other benign lesions. These mimickers include liposarcoma (fat-predominant AML) and leiomyoma (muscle-predominant AML).[13]

Among the benign entities, vascular malformations need to be included in the differential diagnosis; when the vascular feature predominant AML is recognized.[43] Recognition of the variants of AML is helpful in differentiating them from other more common tumors of tubular origin such as renal cell carcinoma (epithelioid AML), and oncocytoma (oncocytoma-like AML). The morphologic features of all described subtypes of AML in this paper are summarized in **Table 1**.

Fortunately, the expression of a variety of muscle specific, vascular and melanocytic markers provide an invaluable tool in establishing the correct diagnosis, when AML mimickers are morphologically suspected.[44]

Table 1. Comparing the variants of AML.

Variant	Morphologic features	Mimicker	Ancillary studies*
Classic AML	Smooth muscle cells radiating from thick walled blood vessels and mature adipose tissue		SMA, MSA, HMB45, Melan-A
Epithelioid AML	Polygonal cells with densely eosinophilic cells, variable nuclear atypia, scant adipose tissue	Renal cell carcinoma, clear cell type, epithelioid leiomyosarcoma, MFH, metastatic melanomas	SMA, HMB45, Epithelial markers, CD10, Vimentin, S-100
Oncocytoma-like AML	Medium to large polygonal eosinophilic cells	Oncocytoma	HMB45, Epithelial markers
Leiomyoma-like AML	Predominantly elongated cells with eosinophillic cytoplasm and oblong nuclei, less prominent vascular and fat component	Leiomyoma	HMB45, SMA, desmin
Liposarcoma-like AML	Mature adipocytes, plump epithelioid cells lining small caliber vessels	Lipoma Liposarcoma	HMB45
AML with epithelial cysts (AMLEC)	Multiple cysts lined by epithelium with cambium-like condensation of small stromal cells beneath the epithelium, thick and tortuous blood vessels	Cystic variants of renal cell carcinoma, simple renal cysts, adult polycystic kidney disease	HMB45, CD10

*MSA: muscle specific actin; SMA: smooth muscle actin; HMB45: human melanoma black 45; MFH: malignant fibrous histiocytoma.

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