Epithelioid Angiomyolipoma
A Morphologically Distinct Variant That Mimics a Variety of Intra-abdominal Neoplasms

Ozgur Mete, MD; Theodorus H. van der Kwast, MD, PhD

This review examines the histopathologic, immunohistochemical, ultrastructural, and molecular biologic features of epithelioid angiomyolipoma (EAML), with an emphasis on the differential diagnosis of intra-abdominal EAML. Epithelioid angiomyolipoma is an uncommon mesenchymal tumor with malignant potential, frequently associated with tuberous sclerosis complex. Histologically, EAML is characterized by sheets or nests of large polygonal epithelioid cells with abundant eosinophilic or occasionally clear cytoplasm, often with prominent nucleoli, and EAML may include multinucleated and markedly pleomorphic forms. As these tumors share a distinctive perivascular epithelioid cell phenotype, they belong to the PEComa tumor family. Nearly all EAMLs show immunoreactivity for both melanocytic and myoid markers. Ultrastructurally, EAMLs show evidence of melanogenesis by the presence of premelanosomes. Epithelioid angiomyolipoma can pose significant diagnostic challenges as it mimics morphologically a variety of neoplasms including renal cell carcinoma, renal oncocytoma, adrenal cortical neoplasm, epithelioid smooth muscle tumor, epithelioid peripheral nerve sheath tumor, epithelioid gastrointestinal stromal tumor, epithelioid melanoma, hepatoblastoma, and hepatocellular carcinoma. The variation in immunophenotype in these tumors requires a prudent use of immunohistochemistry, which may occasionally need complementation by electron microscopy to establish the correct diagnosis.

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Originally believed to be a hamartomatous lesion, angiomyolipoma (AML) is currently defined as a benign mesenchymal tumor composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels.1–4 Although most AMLs arise in kidney, extrarenal AMLs are described in various sites such as retroperitoneum, liver, lung, uterus, vagina, ovary, colon, lymph nodes, skin, bone, nasal cavity, oral cavity, and adrenal gland.2,3 The epithelioid variant of AML (epithelioid angiomyolipoma [EAML]) was first described in 1995 by Martignoni et al as a distinct clinicopathologic variant of AML which is primarily characterized by a predominance of epithelioid cells.1–4,8 Epithelioid angiomyolipomas mimic a variety of other epithelioid neoplasms and they are more often associated with the tuberous sclerosis complex and EAMLs are now considered a potentially malignant neoplasm.1–4 Angiomyolipomas, including its epithelioid variant, belongs to the family of tumors with perivascular epithelioid differentiation, that is, PEComas, which include clear cell myomelanotic tumor of the falciform ligament, ligamentum teres, and common bile duct; lymphangio(leio)myomatosis; pulmonary and extrapulmonary clear cell “sugar” tumors; and a group of rare, morphologically and immunohistochemically similar lesions seen at other sites.1–4

CLINICAL AND RADIOLOGIC FEATURES

Clinical features may vary depending on the presence or absence of TSC, which is characterized by a multisystem genetic disease that can manifest with mental retardation, autism, seizures, and tumors in the brain and in other vital organs such as the kidneys, heart, eyes, lungs, and skin.5,6,10 Angiomyolipomas account for approximately 1% of surgically removed renal tumors.1 They are usually solitary, whereas in TSC they are commonly multiple and bilateral. The reported incidence of AML in patients with TSC is 50% to 90%.9 About 7% of patients with renal AMLs and 5% to 10% of those with hepatic AMLs have TSC.2 In contrast to the classical variant of AML, about 27% of patients with EAML have a history of tuberous sclerosis, while 6.7% of patients with classical AML have TSC.4,10 Both sexes are equally affected by AML and the mean age at diagnosis is 38 years.1–4 Pediatric AMLs, especially in prepubertal children, are practically nonexistent in the absence of TSC, and their identification should prompt the search for other stigmata of this disease complex. The kidney is the most common site of origin for classical and epithelioid AMLs. Intra-abdominal AMLs are usually asymptomatic, often incidentally found during radiography, but some patients may present with abdominal discomfort, flank pain, or hematuria. Renal AMLs larger than 4 cm are at risk for a potentially massive hemorrhage either spontaneously or with minimal trauma.
and the latter can be fatal due to hemorrhagic shock. The demonstration of fatty attenuation in a renal tumor on computed tomography scanning studies is virtually diagnostic of classical AML characterized by a high fat tissue component. However, tumors composed predominantly of smooth muscle cells or epithelioid cells such as EAML radiologically closely mimic renal cell carcinoma (RCC) in the kidney and hepatocellular carcinoma (HCC) in the liver because of the paucity of the adipose tissue component. Moreover, simultaneous occurrence of AML with RCC and oncocytoma in the same kidney has also been reported.

**GROSS PATHOLOGIC FEATURES**

Angiomyolipomas are grossly heterogeneous and composed of an intimate admixture of vessels, smooth muscle, and fat. Therefore, the gross appearance depends on the relative amounts of the various components. Renal AMLs may arise in the renal cortex or medulla and they are well demarcated from the adjacent kidney parenchyma. Angiomyolipomas are slow-growing and usually exhibit expansile rather than infiltrative growth, with the possible exception of some epithelioid variants that may extend and bulge into the perirenal soft tissue. Moreover, atypical features such as vena cava or renal vein involvement have also been reported in EAMLs. Although the color of classical AMLs varies from yellow to tan, depending on the tissue component, EAMLs are usually grey-tan to white and they may contain areas of necrosis. Classical AMLs can exhibit areas of cystic hemorrhagic degeneration and they may simulate clear cell RCC because of the admixture of yellow (fat component) and hemorrhagic cystic areas (blood vessels and degeneration). Most renal AMLs are small and single, but they can vary in size from a few millimeters to larger than 30 cm. Renal EAMLs are usually larger (mean size, 8.6 cm) when compared with their classical counterpart (mean size, 5.6 cm).

**HISTOPATHOLOGIC FEATURES**

Apart from the classic variant, other rare morphologic variants such as epithelioid, atypical, oncocytic, clear cell, and cystic variants are described. The classic triphasic histology of AML demonstrates a variable mixture of mature adipose tissue, thick-walled poorly and abnormally organized vessels, and small muscle cells. The lipomatous component is composed of mature adipose tissue, but it may contain vacuolated adipocytes suggestive of lipoblasts. The thick-walled blood vessels lack the normal elastic content. The muscle cells emanate radially from blood vessels and/or exhibit a fascicular growth pattern.

Epithelioid angiomyolipoma is composed predominantly or exclusively of epithelioid cells (Figures 1, A, 2, A, and 3, A). There are no definite data in the literature regarding the required amount of epithelioid component to designate an AML as EAML. Recently, Aydin et al investigated clinicopathologic features of 194 renal AML cases with emphasis on the epithelioid histology and they arbitrarily set the minimum at 10% to define an AML as EAML. In their large series, EAML was identified in 8% of cases and the mean epithelioid component was 51%. Only 1% of their series represented pure EAML composed of 100% epithelioid component.

The epithelioid cells are typically characterized by polygonal cells with clear to eosinophilic cytoplasm and round to oval nuclei with enlarged vesicular nuclei often with prominent nucleoli and varying degree of nuclear atypia (Figures 1, A, 2, A, and 3, A). The term atypical AML is used to define a pleomorphic variant of EAML. As EAMLs are rare, there are also no definite data regarding the histologic spectrum of EAML in the literature. However, Aydin et al categorized histologically the epithelioid cells into 3 types such as small, intermediate, and large cell types, based on the cell size. Small-type epithelioid cells were relatively uniform in size and had a moderate amount of clear to lightly eosinophilic cytoplasm. The nuclei were in general uniform, although occasional atypical nuclei were usually present. In contrast, large-type epithelioid cells were pleomorphic with abundant, deeply eosinophilic cytoplasm and striking nuclear atypia often associated with hyperchromasia and multinucleation (Figure 3, A and B). Multinucleated and enlarged ganglion-like cells may also be present (Figure 1, A). A population of scant spindle cells can be observed. Epithelioid angiomyolipomas may exhibit necrosis, nuclear anaplasia, mitotic activity, and infiltration of perirenal fat tissue.

Interestingly, intraglomerular lesions, which are composed predominantly of epithelioid smooth muscle cells with features overlapping those of AML, have been reported in patients with or without TSC. These lesions are regarded as precursor lesions.

Epithelioid angiomyolipoma is considered a potentially malignant neoplasm with a distinct risk of metastatic behavior, particularly in those cases showing marked nuclear atypia, severe pleomorphism, and necrosis. A significant correlation with subsequent aggressive behavior was seen for tumors larger than 5 cm with infiltrative growth pattern, high nuclear grade, necrosis, and mitotic activity greater than 1 per 50 high-power fields.

**IMMUNOHISTOCHEMICAL FEATURES**

Angiomyolipomas are typically positive for HMB-45 antibody raised against melanosome-related antigen (Figure 1, B). They are also known to be positive for other melanocytic markers such as HMB-50, Mart-1/Melan-A, tyrosinase, and microphthalmia-associated transcription factor (Figure 1, C). Other markers for AML are CD63 and CD117. Angiomyolipomas exhibit variable immunopositivity for myoid markers such as smooth muscle actin, muscle-specific actin, desmin, and calponin (Figures 1, D and 2, B). Desmin is less often positive, and myoid markers are less frequently expressed in epithelioid and plump spindle cells. About 25% of AMLs express estrogen and progesterone receptors.

Angiomyolipomas are typically negative for S100 protein and epithelial markers such as cytokeratin and epithelial membrane antigen. Compared with renal AMLs, hepatic AMLs much more frequently show a prominent component of large epithelioid cells and are negative for HepPar-1 and low-molecular-weight keratin (Figure 2, C). However, it is worth stressing that CAM 5.2 (low-molecular-weight keratin) may occasionally be positive, albeit focally, in EAMLs. Although infrequent, some AMLs may lack HMB-45 expression, but they do express other melanocytic and myoid markers. Indeed, Aydin et al reported that no melanoma marker is positive in all EAMLs, but the combination of HBM-45 and Melan-A was found to be positive in 100% of the cases. Further, less
than 40% of EAMLs may have exclusive cytoplasmic S100 staining without nuclear staining, a pattern different from melanomas.

ULTRASTRUCTURAL FEATURES

Ultrastructurally, epithelioid cells in AML show evidence of melanogenesis by the presence of intracytoplasmic membrane-bound dense bodies, crystalloids, or granules consistent with premelanosomes (Figure 4). Although some spindle cells reveal features of smooth muscle cells, others contain cytoplasmic lipid droplets indicating the possibility of a transition phenomenon to adipocytes.

DIFFERENTIAL DIAGNOSIS

Oncocytic and clear cell variants of EAMLs can be easily misinterpreted as RCC, renal oncocytoma (RO), or adrenal cortical neoplasm in the renal and adrenal region. Other tumors that enter in the differential diagnosis of EAML are primary or metastatic malignant melanoma, epithelioid smooth muscle tumor, epithelioid peripheral nerve sheath tumor, epithelioid gastrointestinal stromal tumor (GIST), hepatoblastoma, and HCC.

Expression of melanocytic markers and myoid markers combined with the lack of immunoreactivity for cytokeratins and epithelial membrane antigen argue against the diagnosis of RCC, RO, and HCC (Table). Some RCCs, particularly those with t(6;11) translocation characterized by a dimorphic morphology, may be negative for epithelial membrane antigen, while exhibiting melanocytic antigens. Demonstration of nuclear staining for transcription factor-EB protein may be helpful to differentiate t(6;11) translocation-type RCC from EAML. Similarly, RCC associated with t(X;1p11)/TFE3 translocation may rarely be positive for HMB-45/Melan-A and negative for cytokeratin; the latter should be differentiated based on histology and by the demonstration of TFE3 protein expression.

Eosinophilic variants of RCC and RO have several morphologic features in common with EAML, but they can be distinguished by using melanoma markers and staining for keratins (Table). Particularly, diffuse staining...
Figure 2. Epithelioid hepatic angiomyolipoma. A, Epithelioid tumor cells (hematoxylin-eosin, original magnification ×40). B, Variable smooth muscle actin positivity in the tumor cells (original magnification ×40). C, HepPar-1 immunoreactivity in the entrapped nontumorous hepatocytes; epithelioid angiomyolipoma is totally negative (original magnification ×20).

Figure 3. Retroperitoneal large-cell variant of epithelioid angiomyolipoma. A and B, Varying proportions of large epithelioid cells with nuclear hyperchromasia, adipose tissue, scant spindle cells, and abnormal vascular structures (hematoxylin-eosin, original magnifications ×20 [A] and [B]).

Figure 4. Epithelioid angiomyolipoma. Electron microscopic examination reveals that tumor cells contain numerous premelanosomes (original magnification ×5000).
for CAM 5.2 for an ambiguous lesion in a needle biopsy virtually excludes a diagnosis of EAML because it is mostly negative or occasionally displays only focal expression for this keratin.

Although EAMLs are rare in the adrenal gland, this entity should be considered in the differential diagnosis of adrenal cortical adenoma and carcinoma. Therefore, it is important to note that Melan-A (clone A103), representing a well-established adrenal cortical marker, is expressed particularly in EAML. However, EAML can be distinguished by the demonstration of other melanocytic antigens (HMB-45) and muscle markers. However, absence of HBM-45 does not completely rule out the possibility of EAML. Further, adrenal cortical carcinomas are usually negative for keratins, but approximately 10% can be CAM 5.2 positive. The positivity for other adrenal cortical markers such as α-inhibin, calretinin, synaptophysin, and steroidogenic factor 1 or the absence of premelanosomes can be of additional help for the differentiation of adrenal cortical neoplasm from EAML.

Compared with renal AMLs, hepatic AMLs much more frequently show a prominent component of large epithelioid cells, and a considerable proportion of hepatic AMLs are composed nearly exclusively of such cells (Figure 2, A). The primary differential diagnosis of hepatic EAML is with HCC and epithelioid leiomyosarcoma. Trabecular and sinusoidal pattern similar to HCC has also been reported in hepatic AMLs. Other tumors that may be confused with hepatic AML include hepatoblastoma, which is mainly seen in childhood. Staining for HepPar-1 and low-molecular-weight keratin can thus be useful in the differential diagnosis of primary and metastatic HCC (Figure 2, C).

Epithelioid angiomyolipomas are typically negative for S100 protein; however, less than 40% of EAMLs may have cytoplasmic S100 without nuclear staining, a pattern different from melanomas. Malignant melanomas may rarely lack S100 staining, and in such cases their distinction from EAML depends on additional markers, most notably myoid markers. As for renal tumors, it is of interest that S100A1 protein is consistently expressed in ROs and is generally negative in chromophobe RCC, while variably positive in other RCC subtypes.

Epithelioid GIST, other epithelioid mesenchymal tumors, and epithelioid malignant melanomas are in the differential diagnosis of EAML. In cases of GIST with fewer than 50% of tumor cells being CD117+, the use of melanocytic markers is mandatory and might help to reach the correct diagnosis because GISTs are negative for melanocytic markers. Notably, melanomas and eosinophilic renal epithelial tumors may also express CD117.

Although immunohistochemistry plays a major role in the differential diagnosis of EAML, extensive sampling of the tumor is also recommended to look for abnormal blood vessels and intratumoral fat (Figure 3, A and B).

MOLECULAR BIOLOGIC FEATURES

Because AML and EAMLs are associated with TSC, the (germ-line) genetic changes characteristic of TSC will be found in these tumors. Tuberous sclerosis is an autosomal dominant inherited disorder with a high penetrance and variable expression. Tuberous sclerosis complex is characterized by germ-line mutations in the TSC1 or TSC2 genes located on chromosomes 9q34 and 16p13.3, which encode the proteins hamartin and tuberin, respectively. The TSC2 gene encodes tuberin, a 180-kDa GTPase-activating protein for RAP1 and RAB5. Tuberin and hamartin interact with each other and form a cytoplasmic complex. Frequent loss of heterozygosity of variable portions of the TSC2 gene locus (16p13, tuberin) is demonstrated in inherited and sporadic AML cases. Tuberin is a member of the cell signaling pathway involved in RNA translation (mTOR pathway), providing a potential therapeutic target using the drug sirolimus that suppresses mTOR signaling. It has been suggested that p53 has a specific role in malignant progression of AML because a few case reports demonstrated TP53 mutation exclusively in the epithelioid cells of AML.

TREATMENT AND PROGNOSIS

Most AMLs follow a benign course and patients are usually treated conservatively by ultrasonography imaging at regular intervals. When patients have recurrent episodes of hemorrhage or massive bleeding, the tumor may need resection. Renal arterial embolization may be used to control hemorrhage. For suitable patients in whom the diagnosis of renal AML is not established with radiologic findings, partial nephrectomy enables pathologic diagnosis with a minimal loss of function. Nephron-sparing surgery is of even greater importance in patients with tuberous sclerosis because their tumors are often multifocal and bilateral. Hepatic AMLs are also managed conservatively or by local resection.

During sirolimus therapy, AMLs showed signs of regression, but they tended to increase in size after the
therapy was stopped. Additional studies evaluating drug safety are needed to determine if and how mTOR inhibitors should be incorporated into standard AML treatment.

In contrast to the usually benign classic AML, malignant behavior, including local recurrence and distant metastasis, has been reported in approximately one-third of EAMLs. Moreover, several cases of otherwise classic renal AML have been associated with epithelioid or sarcomatoid transformation and subsequent malignant behavior. Metastatic lesions have been reported in AMLs that have not been established universally, but a potential for malignant behavior should be anticipated for AMLs that are highly pleomorphic, are mitotically active, or have necrosis, prominent epithelioid or sarcomatoid areas, and infiltrative growth pattern. 

**CONCLUSION**

Epithelioid angiomyolipoma represents a distinct diagnostic entity and may occur at diverse visceral and somatic soft tissue sites. It mimics morphologically a variety of neoplasms such as RCC, RO, adenocortical neoplasm, epithelioid smooth muscle tumor, epithelioid peripheral nerve sheath tumor, epithelioid GIST, epithelioid melanoma, hepatoblastoma, and HCC. This differential diagnosis can be particularly problematic in small biopsies and sometimes even in surgical specimens. Morphologic clues to diagnosis such as islands of mature fat and abnormal vessels should be diligently looked for in surgical specimens. A correct diagnosis of EAML may require prudent use of immunohistochemistry (Table).

Due to the variation in immunohistochemical phenotype, ultrastructural analysis may occasionally be of help to establish the diagnosis. The recognition of EAML is important because it is also considered a potentially aggressive neoplasm, epithelioid smooth muscle tumor, epithelioid sarcoma, renal AML have been associated with epithelioid or sarcomatoid transformation and subsequent malignant behavior. Metastatic lesions have been reported in AMLs that have not been established universally, but a potential for malignant behavior should be anticipated for AMLs that are highly pleomorphic, are mitotically active, or have necrosis, prominent epithelioid or sarcomatoid areas, and infiltrative growth pattern. 

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**References**


