Epithelioid Angiomyolipoma: An Overview of Five Cases with the Concept of PEComa

HOU-CHI HWANG1 JEN-I HWANG1,3,4 SIU-WAN HUNG1,5 MEIN-KAI GUENG1 CHI-SHUENN YANG7 CLAYTON CHI-CHEH HANG 6,7

Department of Radiology1, Department of Pathology2, Taichung Veterans General Hospital
Faculty of Medicine3, National Yang Ming University
Faculty of Medicine4, Faculty of Medical Imaging & Radiological Sciences5, Chung Shan Medical University
Department of Radiological Technology6, Central Taiwan University of Science and Technology
Department of Physical Therapy7, Hungkuang University

Angiomyolipoma is a well-known rare soft tissue tumor involving the kidneys, liver and other organs. Long believed to be a benign hamartoma, angiomyolipoma is now considered a neoplasm that arises from perivascular epithelioid cell. Epithelioid angiomyolipoma is potentially malignant variant of angiomyolipoma characterized by epithelioid cells that mimic malignant tumors arising from the organs. Immunoreactivity with HMB-45 is helpful for its identification. It is now considered to be a part of PEComa family and perivascular epithelioid cells (PEC) are recently proposed to be its most common progenitor cells.

Here we give an overview of five rare cases with epithelioid angiomyolipoma, one in left upper retroperitoneum, two in liver and two in kidney, focusing on clinical presentations and imaging findings. The case in left upper retroperitoneum was pre-operative differentiated from retroperitoneal liposarcoma due to huge space-occupying lesion of uncertain origin. The two cases in kidneys were clinically manifested as palpable abdominal mass and/or acute abdominal pain; both were pre-operative diagnosed by tumoral fat content and/or the classic clinical features. One case with malignant epithelioid angiomyolipoma of kidney associated with tuberous sclerosis (TS) developed metastases to liver and retroperitoneum and finally died of the disease. The two cases of hepatic epithelioid angiomyolipoma were pre-operative mis-diagnosed as hepatocellular carcinoma (HCC) due to its rare incidence and less fat component of the tumor with similar imaging finding to HCC.

In conclusion, we radiologists should be aware of the existence of rare epithelioid variant of angiomyolipoma which belongs to the PEComa family arising in different origins and its potential malignant behavior.

Angiomyolipoma (AML) is a histologically complex mesenchymal tumor with a proliferation of thick-walled blood vessels, adipose tissue and smooth muscle-like cells. The kidney is the most common primary site for AML, although the involvement of extrarenal sites including retroperitoneum has occasionally been described [1, 2]. Long believed to be a benign hamartoma, angiomyolipoma is now considered a neoplasm that arises from perivascular epithelioid cell. Epithelioid angiomyolipoma is a rare variant of angiomyolipoma characterized by epithelioid cells that mimic renal cell carcinoma and is potentially malignant. Immunoreactivity with HMB-45 is helpful for its identification [3]. Here we present the clinical and imaging findings of five rare cases of epithelioid angiomyolipoma.

Case 1

A 27-year-old man without a history of tuberous sclerosis (TS) suffered from increased abdominal
girth for 6 months. Computed tomography (CT) scan of the abdomen showed a huge mass with heterogeneous enhancement of solid component and multiple cystic changes, occupying left upper abdomen and causing downward displacement of left kidney (Fig. 1a). Digital subtraction angiography (DSA) showed a huge hypervascular tumor with multiple engorged tortuous feeding arteries from the splenic, the great pancreatic, the inferior adrenal and the left renal arteries (Fig. 1b). Microaneurysms as a feature of angiomyolipoma on DSA (Fig. 1b) were also depicted. It was pre-operative differentiated from left adrenal mass or retroperitoneal liposarcoma presenting as a huge space-occupying lesion of uncertain origin. He then received surgery for tumor removal, left radical nephrectomy and left adrenalectomy. Pathologic diagnosis showed epithelioid variant angiomyolipoma of retroperitoneum with free resection margin, but multifocal tumor necrosis were also noted. Left kidney and left adrenal were not involved. Follow-up condition remained fair for two years.

**Case 2**

A 74-year-old man without a history of TS suffered from sudden onset of abdominal pain with hypovolemic shock. CT scan of the abdomen showed a cystic tumor measured 20cm in size over lateral lower border of the right kidney with cystic hemorrhage (Fig. 2a). It caused upward displacement of the right kidney (Fig. 2b). Emergent DSA was performed for possible embolization of active bleeders, and showed multiple tortuous feeding arteries from right renal artery (Fig. 2b). Due to less amount of fat content but marginal enhancement, it was pre-operative differentiated from ruptured cystic renal cell carcinoma (RCC). Successful therapeutic embolization and surgery of right radical nephrectomy were performed. Pathologic diagnosis disclosed epithelioid variant angiomyolipoma of right kidney. Follow-up condition remained uneventful for four years.

**Case 3**

A 30-year-old man with a history of TS suffered from malignant epithelioid angiomyolipoma, initially manifesting as palpable masses with bilateral renal AMLs, epithelioid type, as surgical biopsy proved.

Eighteen months after the surgery, due to symptomatic flank pain, a follow-up CT scan revealed bilateral renal masses with fat content, heterogeneous enhancement of solid portion and cystic changes as tumor necrosis and hemorrhagic foci (Fig. 3a). Tumor invasion to right psoas muscle, ascending colon, cecum and terminal ileum were also noted (Fig. 3b). He then received surgical treatment of right nephrectomy and right hemicolectomy. Pathology confirmed the diagnosis of epithelioid AML with extensive necrosis and tumor involvement to right psoas muscle, ascending colon, cecum and

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**Figure 1.** A 27-year-old male with epithelioid angiomyolipoma over upper pole of left kidney. **a.** Axial contrast-enhanced CT image showed a big mass (arrows) with heterogeneous enhancement of solid component and multiple cystic changes, occupying left upper abdomen. **b.** DSA showed a big hypervascular tumor with multiple engorged tortuous feeding arteries from splenic (not shown), great pancreatic (not shown), left inferior adrenal (lia) and branches of left renal (blr) arteries. Microaneurysms (arrowhead) were also noted as a feature of angiomyolipoma. The tumor caused downward displacement of the left kidney (arrows).
terminal ileum as multicentric involvement or tumor metastases were considered.

Two years later, post-contrast CT scan showed multiple heterogeneous less-enhanced metastases in right lobe of liver (Fig. 3c) as confirmed by pathology. DSA showed hypervascularity of the lesions in left kidney and right lobe of liver. Tortuous feeding arteries with microaneurysms were noted (Fig. 3d). He then received right heptectomy for the liver metastases. Pathological study showed epithelioid AML which was characterized by HMB-45 immunoreactivity (Fig. 3e, 3f). Metastatic malignant epithelioid AML was diagnosed.

However, 6 months later, post-contrast CT scan (not shown) revealed recurrent metastases at porta hepatitis causing biliary obstruction. Multiple mesenteric metastases with involvement to right psoas muscle were also noted. The patient finally died on cardiopulmonary failure and malnutrition.

**Figure 2.** A 74-year-old man with epithelioid angiomyolipoma over lower pole of right kidney. He suffered from sudden onset of abdominal pain with hypovolemic shock. **a.** Precontrast (upper row) and postcontrast (lower row) images of axial abdominal CT scan showed a big cystic tumor (arrows) over lateral lower border of the right kidney (*) with cystic hemorrhage (ch) and enhanced mural solid component (arrowhead). **b.** Emergent DSA was performed for possible embolization of active bleaders, and showed multiple tortuous feeding arteries (*) from right renal artery (rra). It caused upward displacement of the right kidney (arrows). Microaneurysms (arrowheads) were also noted as a feature of angiomyolipoma.

**Case 4**

A 47-year-old man without the TS history initially suffered from post-prandial abdominal fullness for 2 years. Ultrasonography (Fig. 4a) showed a well-defined heterogeneously hyperechoic mass with hypervascularity in left lobe of liver. Dynamic enhanced CT scan of the abdomen (Fig. 4b) showed a well-defined hypervascular tumor with slight hypodensity on the portal venous phase. Engorged feeding arteries were centrally located. DSA further demonstrated tortuous engorged feeding arteries to the tumor. These features of hepatic angiomyolipoma were subtle and difficult to be differentiated from HCC (especially in those with fatty metamorphosis) in the pre-operative diagnosis. He then received surgical tumor removal. Pathologic study showed that the tumor was predominantly composed of epithelioid cell in more than 90% of the tumor. Cellular pleomorphism and mild cellular atypia were seen, but no significant mitoses or angiolymphatic perme-
Figure 3. A 30-year-old male with malignant epithelioid angiomyolipoma of both kidneys with liver metastasis. He initially manifested as palpable masses with bilateral renal AMLs, epithelioid type, as surgical biopsy proved. a. and b. 18 months later, due to symptomatic flank pain, follow-up axial CT scan revealed bilateral renal masses (arrows) with fat content (f), heterogeneous enhancement of solid portion and cystic changes (*) as tumor necrosis and hemorrhagic foci. Tumor invasion to right psoas muscle (p), A-colon (arrowhead), cecum and terminal ileum as multifocal tumors or metastases. c, d. 2 years later, post-contrast axial CT scan (c) showed multiple heterogeneously less-enhanced metastases (arrows) in right lobe of liver as confirmed by pathology. DSA (d) showed hypervascularity of the lesions in right lobe of liver. Tortuous feeding arteries (*) with microaneurysms (arrowheads) were noted. e, f. Microscopically (e), the tumor is composed of monotonous epithelioid cells with nuclear pleomorphism (400×). Immunohistochemically (f), the tumor cells showed strong HMB-45 cytoplasmic reaction (100×).

Figure 4. A 47-year-old male with epithelioid angiomyolipoma in left lobe of liver. He initially suffered from post-prandial abdominal fullness. a. Ultrasonography showed a well-defined heterogeneously hyperechoic mass (arrows) in left lobe of liver with hypervascularity (arrowheads) detected as flowing signals on color Doppler. b. Images of dynamic contrast-enhanced abdominal CT scan during the arterial phase (upper) and the portal venous phase (not shown) show a well-defined hypervascular tumor (arrows) with slight hypodensity on portal venous phase. Engorged feeding arteries were centrally located (arrowheads). These features of hepatic angiomyolipoma were subtle and difficult to be differentiated from HCC (especially in those with fatty metaplasia) as pre-operative diagnosis.
Epithelioid angiomyolipoma

Tumor cells were stained strongly positive for HMB-45. The pathologic diagnosis was epithelioid variant of hepatic angiomyolipoma. Follow-up condition remained uneventful for two years.

Case 5

A 46-year-old woman without a history of tuberous sclerosis (TS) suffered from epithelioid angiomyolipoma in right lobe of liver. She initially presented with complaints of abdominal fullness. Dynamic enhanced CT scan for the liver (Fig. 5a) showed a well-defined hypervascular tumor with less-enhanced necrotic components on venous phase. Engorged feeding arteries were centrally located. DSA further demonstrated engorged tortuous feeding arteries arising from right hepatic, right inferior phrenic (Fig. 5b), and capsular branches of right renal arteries with microaneurysms (Fig. 5b) within the tumor. These features of hepatic angiomyolipoma were subtle and similar to HCC (especially in those with fatty metamorphosis) in the pre-operative diagnosis. Pathologic study of surgically removed tumor showed epithelioid tumor cells with infiltrative growth pattern and nuclear pleomorphism, accompanying with tumoral hemorrhage and necrosis without fat content. Tumor cells were stained strongly positive for HMB-45. Pathologic diagnosis was epithelioid variant of hepatic angiomyolipoma. Follow-up condition remained stable for more than two years.

DISCUSSION

Angiomyolipoma (AML) is a histologically complex mesenchymal tumor with a proliferation of thick-walled blood vessels, adipose tissue and smooth muscle-like cells. The kidney is the most common primary site for AML, although the involvement of extrarenal sites including retroperitoneum has occasionally been described [1, 2]. Epithelioid AML, characterized by the proliferation of predominant epithelioid cells [4], usually has pleomorphic cytomorphology.

In 1992 Bonetti et al. [5] described a special group of cells, perivascular epithelioid cells (PEC) which stained positively with melanosomal marker HMB-45. Following this, Zamboni et al. [6] in 1996 coined the term ‘PEComa’ to encompass a group of related mesenchymal tumours containing these PEC. These tumours included renal and extra-renal angiomyolipoma (AML), lymphangiomyomatosis, clear cell sugar tumor of the lung (CSST), extrapulmonary ‘sugar’ tumor, and a group of lesions arising at various visceral and soft-tissue sites, which are morphologically and immunophenotypically similar. Almost all of these tumours show immunoreactivity for both the melanocytic (HMB-45 and/or melanin A) and smooth muscle (actin and/or desmin) markers. The clinical behavior of PEComas varies, from being completely benign (e.g. CSST) to frankly malignant.
(malignant epithelioid AML, MEAML) [6].

PEComas occur predominantly in females, and can arise from the gastrointestinal, urinary or female genital tracts (uterus, ovaries and broad ligament), retroperitoneum, abdomino-pelvic sites, somatic soft tissues and skin.

Based on these findings, it is evident that renal AML is not one entity but a spectrum of tumours that can be subclassified as ‘classical (CAML)’ and epithelioid (EAML) AML. The latter is further subclassified as atypical AML (AAML) and MEAML [7].

AAML is a highly cellular and polymorphic lesion that showed scanty adipose tissue and lacks a well-developed smooth muscle component. The typical thick-walled tortuous vessels of CAML are rarely found in AAML.

MEAML is a rare tumor of the kidney first reported in 1998; Pea et al. [8] proposed that this malignant variant should be termed MEAML. Only a few cases of MEAML have been reported. The criteria for distinguishing benign from MEAML are not yet clearly defined, but a high mitotic index and tumor size should be considered as important indicators of a malignant behavior [9]. We here added a case of MEAML of the kidney in this case series.

The histological, immunohistochemical and ultrastructural features of AAML/MEAML suggest that the constituent cell of this lesion is a unique vascular smooth muscle cell/ pericyte capable of undergoing phenotypic transformation from developmentally dysplastic through intermediate phenotypes to more differentiated spindled phenotypes. Thus AAML/EAML can be regarded as unusual tumours of the kidney, which show phenotypic overlap between carcinoma and AML [7].

Extrarenal angiomyolipomas are rare and are also considered a reflection of multicentricity rather than of true metastasis [10, 11]. Multicentricity of the angiomyolipoma is thought to be caused by either the congenital presence of cell precursors in multiple sites or a form of benign metastases similar to that in benign metastasizing leiomyoma [11]. With the concept of PEComa, it is not surprising that AML can arise from many anatomic sites other than kidney, and that some cases of its epithelioid variant are reported having malignant clinical behaviors [9].

Microscopically, the diagnosis of typical AML is usually easy because of its composition of abnormal blood vessels, smooth muscle, and fat in varying relative proportions. However, immunohistochemistry can be important for diagnosis of atypical AML or epithelioid-type AML [8, 12].

In imaging study of angiomyolipomas, due to the fact that variable fatty content ranging between 5% and 90%, and its multicentricity arising from various anatomic sites, the preoperative radiological diagnosis of AMLs with atypical histological features poses a diagnostic challenge, especially in absence of radiographically evident fat. Thus, under histological classification of AMLs into CAML and EAML, according to different anatomic origins, the imaging differential diagnosis of AMLs can put into two categories: classic triphasic type and atypical fat poor type, based on the presence or absence of fat.

Concerning renal AML of classic triphasic type, the preoperative diagnosis is relatively easy by macroscopic fat content. The presence of macroscopic fat on CT or MRI is characteristic of AMLs. Loss of signal intensity on frequency-selective fat-suppressed MRI definitively identifies macroscopic fat [13]. The most important differential diagnosis is the rare incidence of RCC with intratumoral fat because of different treatment between AMLs and RCCs. In the study of Hélénon et al. [14], malignancy should be suspected on the basis of the following criteria: presence of intratumoral calcifications; large, irregular tumor invading the perirenal or sinus fat; large necrotic tumor with small foci of fat; and association with nonfatty lymph nodes or venous invasion.

As for renal AML of fat poor type, it is indistinguishable from RCC on imaging studies alone. Recent studies indicate that in contrast to RCCs, AMLs with minimal fat show uniform, prolonged contrast enhancement and a higher signal intensity index on double-echo, chemical shift FLASH MRI [13].

Regardind to hepatic AML, it is composed of both soft tissue and fat components on CT scan. The density of the lesion depends on the relative proportion of the tissue components. Classic triphasic angiomyolipomas with an abundant fat component are hypointensuring on noncontrast CT, with absent or minimal enhancement after contrast material injection, whereas they are typically hyperintense on both T1- and T2-weighted MR sequences. On imaging studies, such lesions are almost indistinguishable from myelolipomas and lipomas [15]. Angiomyolipomas with a small fat component are often difficult to diagnose on imaging studies, sometimes difficult to differentiate from other benign tumors of the liver or, in certain instances, from hepatocellular carcinomas with fatty metamorphosis [15].

However, there are some useful imaging features to characterize hepatic AMLs. The first is the
presence of persistent central vascular enhancement on both arterial and portal venous phases of dynamic contrast-enhanced CT scan [16, 17]. The feeding blood vessels can be seen in other hypervascular lesions such as HCC and FNH, but the vessels in those cases usually are located in the periphery of the lesions [17]. MRI is also an important diagnostic technique that allows fat suppression and multiphase dynamic contrast-enhanced scanning. Dynamic contrast-enhanced imaging on MRI is similar to that of CT with the central vessels seen in the lesions [17]. The second is early and prolonged enhancement of hepatic AML with its special pattern of time-density (intensity) curve (time to peak enhancement about 40-80s, which is later than that in HCC; prolonged enhancement more than 4 minutes, which is longer than that in HCC) on dynamic study are significant for angiomyolipoma. Thus, preoperative radiologic diagnosis of the hepatic AML may be possible by using CT (including non-enhanced and dynamic CT) and MRI (including T1, T2 spin echo, fat suppression technique, and dynamic MRI) [16]. However, in certain cases, percutaneous biopsy is necessary to reach a definitive diagnosis.

The management of renal AML depends on the size of the lesion, radiological features and histological appearance. Treatment protocols for CAML are well established and entail either observation, embolization, partial or total nephrectomy. Decision-making is relatively easy in most cases because of the classical features on CT. Other tumours, including AAML and MEAML, mimic RCC on imaging findings and hence most patients will require partial or radical nephrectomy. After surgical excision these patients need either a high- or low-intensity follow-up, depending on the pathological findings and tumor size. Larger tumors with a higher mitotic index in particular should be considered malignant and followed accordingly [7]. For AML arising from other sites, surgery seems to be an only effective approach [9].

In conclusion, we radiologists should be aware of the existence of rare epithelioid variant of angiomyolipoma which belongs to the PEComa family arising in different origins and its potential malignant behavior.

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類上皮型血管肌肉脂肪瘤：以血管旁類上皮細胞腫瘤家族觀念綜覧五個病例

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台中榮民總醫院 放射線部 1 病理部 2
陽明大學 醫學系 3
中山醫學大學 醫學系 4 醫影系 5
中台科技大学 放射技術系 6
弘光科技大学 物理治療系 7

血管肌肉脂肪瘤是一種罕見的軟組織瘤，最多起源自腎臟，亦可影響肝臟或身體其他器官。長期以來被認為是一種良性的過誤瘤，但最近幾年來研究認為，這是一種起源自血管旁類上皮細胞的新生性腫瘤。類上皮型血管肌肉脂肪瘤是一種罕見的次分型，是由類上皮細胞所構成，具有潛在可能的惡性表現，臨床上診斷易與其他惡性腫瘤混淆，產生誤診。HMB-45 陽性的免疫組織化學反應為其診斷依據。類上皮型血管肌肉脂肪瘤目前已被歸屬在血管旁類上皮細胞腫瘤家族。

這裡我們描述了五個類上皮型血管肌肉脂肪瘤的病例，其中一例源自左上後腹腔，兩例源自腎臟，兩例源自肝臟，其臨床和影像學的表現如下：

左上後腹腔之病例因腫瘤巨大，在影像上無法確認其起源，故術前必需胸部惡性脂肪肉瘤做鑑別診斷。長於腎腫的兩個病例，其臨床上的表現為腹部可觸到之腫瘤或合併急性腹痛，這兩例皆於術前診斷，因影像上的腫瘤脂肪成分與典型的臨床表現。其中一例長於腎腫的病人合併結節性硬化症，之後發展成肝臟及腹腔轉移，最後死於疾病。長於肝腫的兩個病例，術前皆誤診為肝細胞癌，主因其影像上的表現不具腫瘤脂肪成分，而類上皮型血管肌肉脂肪瘤在肝腫的發生率為罕見所致。

因為近來研究顯示其潛在可能的惡性表現，放射線醫師必須了解此種罕見的類上皮型血管肌肉脂肪瘤之疾病，以利診斷。