Clinical presentation of epithelioid angiomyolipoma

Hang Kye Park,1 Shaozeng Zhang,3 Michael KK Wong2 and Hyung L Kim1

1Departments of Urologic Oncology, 2Medicine, and 3Pathology, Roswell Park Cancer Institute, Buffalo, New York, USA

Objective: Epithelioid angiomyolipomas (AML) of the kidney are malignant tumors with aggressive clinical behavior. Methods: We reviewed cases of epithelioid AML recently diagnosed at our institution to highlight the spectrum of clinical presentations.

Results: In all cases, renal lesions seen on computed tomography were suspicious for renal cell carcinoma (RCC). Histologically, these tumors resemble RCC. The diagnosis of epithelioid AML was established by positive staining for melanoma and smooth muscle cell markers, and presence of perivascular epithelioid cells. One patient presented with a renal tumor extending into the inferior vena cava to the level of the hepatic veins. Two patients developed recurrent, metastatic disease following nephrectomy. One patient with tuberous sclerosis and multiple, bilateral AML developed an enhancing renal tumor that did not contain any fat densities. A partial nephrectomy was performed and pathology revealed epithelioid AML adjacent to conventional AML.

Conclusions: These tumors are distinguished from RCC by positive immunostaining for melanoma markers and smooth muscle cell markers. They resemble conventional RCC on imaging. Epithelioid AML may be locally aggressive and metastasize.

Key words: angiomyolipoma, epithelioid angiomyolipoma, kidney, renal cell carcinoma, tuberous sclerosis.

Introduction

Angiomyolipomas (AML) are considered benign renal tumors, characterized by vascular, smooth muscle and mature adipose elements. The components of AML are thought to arise from unsuppressed and aberrant differentiation of the renal mesenchyma. AML comprise 2.0–6.4% of all renal tumors; however, they represent one of the most common benign renal lesions of the kidney.1–3 AML can occur as an isolated renal lesion or as part of the tuberous sclerosis complex (TSC). Approximately 50% of patients with TSC develop AML, which tend to be bilateral and multifocal.4,5

Rare cases of clinically aggressive or malignant AML have been reported. These atypical variants of AML are histologically categorized as epithelioid AML. These tumors often resemble renal cell carcinomas both radiographically and histologically. It has been suggested that increased incidence of renal cell carcinoma (RCC) associated with TSC may have resulted from the incorrect classification of epithelioid AML as RCC.6 The recent recognition that these tumors express melanocyte markers and smooth muscle cell markers has standardized the histological diagnosis of epithelioid AML.7 These are rare tumors and to our knowledge no series of epithelioid AML has been reported. We describe four cases of epithelioid AML that illustrate the spectrum of associated clinical features.

Methods

Between June 2004 and November 2005, four patients were diagnosed with epithelioid AML at our institution. In accordance with institutional review board protocol, EDR 53605, medical records were reviewed and summarized. Renal tumors were staged according to the 2002 American Joint Committee on Cancer staging manual. Preoperative staging evaluation included computed tomography (CT) of the abdomen/pelvis, chest X-ray and a complete metabolic panel. Table 1 lists the antibodies used for the immunohistochemical analysis. Immunohistochemical analysis was performed using appropriate positive and negative controls. Formalin-fixed, paraffin-embedded samples were stained by immunohistochemistry using avidin-biotin-peroxidase complex.

Results

Table 2 summarizes the patient characteristics. All four patients had renal masses noted on CT scan. None of the lesions contained fat densities on CT and therefore all lesions were considered suspicious for renal cell carcinoma. One patient had a renal mass associated with a tumor thrombus extending into the inferior vena cava to the level of the hepatic veins (Fig. 1). Eight months following surgical resection of epithelioid AML, the patient had recurrence in the liver and peritoneum. Another patient with clinical stigmata of TSC had multiple fat-containing lesions on CT; however, one renal lesion measured 4 cm and did not contain any fat (Fig. 2a,b). Following partial nephrectomy, the histology was epithelioid AML. The specimen contained adjacent lesions consistent with conventional AML containing vascular, smooth muscle and mature adipose elements.

The third patient had epithelioid AML diagnosed after undergoing a laparoscopic partial nephrectomy for an incidentally noted 1.4-cm renal mass. The fourth patient underwent a nephrectomy at another institution and presented approximately 1-year later with multiple liver lesions and extensive adenopathy. A positron emission tomography (PET) scan was positive in the liver and in the area of the axillary, retroperitoneal, pelvic and inguinal lymph nodes. Biopsies of a liver lesion and a retroperitoneal lymph node were consistent with epithelioid AML. Comparison of the biopsy specimen and the original renal lesion revealed identical morphology and immunohistochemical staining pattern. In all cases, pleomorphic, perivascular epithelioid cells (PEC) were noted and the diagnosis was confirmed by staining for melanoma and smooth muscle cell markers (Fig. 3a–c).
The major differential diagnosis based on histological characteristics alone included conventional RCC with sarcomatoid features, metastatic melanoma and epithelioid AML. Additional markers were used to rule out RCC and melanoma. The lack of staining for cytokeratin markers, including cytokeratins AE1/AE3, HMW cytokeratin and cytokeratin CAM 5.2, made conventional RCC unlikely. Metastatic melanoma was ruled out by negative staining for melanoma markers such as S100 and positive staining for smooth muscle actin (SMA; Fig. 3d), HHF-35 and caldesmon.

### Table 1  Antibodies used for immunohistochemistry

| Antibody    | Clone       | Dilution | Pretreatment | Source                        |
|-------------|-------------|----------|--------------|-------------------------------|
| Melanosome  | Monoclonal  | 1:400    | None         | Dako, Carpinteria, CA, USA    |
|             | HMB-45      |          |              |                               |
| Cytokeratin | Monoclonal  | 1:100    | Proteinase K–5 min | Dako                         |
|             | AE1/AE3     |          |              |                               |
| HMW cytoke | Monoclonal  | 1:100    | Proteinase K–5 min | Dako                         |
|             | 34B12       |          |              |                               |
| Cytokeratin | Monoclonal  | 1:100    | Proteinase K–5 min | Neomarker, Fremont, CA, USA  |
|             | CAM 5.2     |          |              |                               |
| S100        | Polyclonal  | 1:4000   | None         | Dako                          |
| SMA         | Monoclonal  | 1:200    | Heat–10 min  | Dako                          |
|             | 1A4         |          |              |                               |
| Muscle actin| Monoclonal  | 1:200    | None         | Dako                          |
|             | HHF-35      |          |              |                               |
| Caldesmon   | Monoclonal  | 1:100    | Heat–10 min  | Dako                          |
|             | h-CD        |          |              |                               |

SMA, smooth muscle actin.

### Table 2  Patients diagnosed with epithelioid angiomyolipoma (AML)

| Case | Age (years) | Sex | TSC | Renal lesion | Symptomatic | Size (cm) | Fat densities (CT finding) | Tumor thrombus | Necrosis | TNM stage | Immunohistochemistry | Recurrence | Status |
|------|-------------|-----|-----|--------------|-------------|-----------|---------------------------|----------------|----------|-----------|----------------------|------------|--------|
| 1    | 69          | Male| No  | No           | No          | 13        | No                        | Yes            | No       | T3bN0M0‡  | HMB-45 Positive       | Liver, peritoneum | Alive  |
| 2    | 37          | Female| Yes | Yes†         | Yes†         | 4         | No                        | No             | No       | T1aN0M0   | Melanin Positive      | None       | Alive  |
| 3    | 45          | Female| No  | No           | No          | 1.4       | No                        | No             | No       | T1aN0M0   | Time to recurrence/length of f/u (months) 8/10 | –/4 | Alive |
| 4    | 46          | Female| No  | No           | No          | 17        | No                        | No             | No       | T2N0M0    | Hetero Non-Melanoma    | Liver, Lymph nodes | Alive  |

†Symptoms resulted from hemorrhage into a 7.5 cm conventional AML. ‡Extension into perinephric fat and extension into the inferior vena cava to the level of the hepatic veins. TSC, tuberous sclerosis complex.

### Discussion

AML have been considered benign lesions that can be diagnosed radiographically.4 Approximately half of AML occur as part of the TSC. AML found in the kidney are generally managed conservatively. Partial nephrectomy or angiographic embolization has been recommended for symptomatic lesions and lesions greater than 4 cm.5,10 Most asymptomatic lesions are followed with interval abdominal imaging. However, 10 cases of metastatic AML have been reported,2,4,11–17 and our study includes two additional cases of metastatic AML (Table 3).
The epithelioid variant of AML has been associated with aggressive clinical behavior, including extension into the vena cava and metastasis. Histologically, epithelioid AML are characterized by large epithelioid cells and paucity of fatty components. These lesions can resemble melanoma or a conventional renal tumor that has a predominance of sarcomatoid elements. The recognition that AML are uniformly positive for melanoma markers such as HMB-45 and melan-A has facilitated proper diagnosis. These tumors may also be focally positive for smooth muscle markers such as SMA.

Pea et al. reviewed five tumors that were previously reported as RCC in patient with TSC. Three of the tumors were positive for HMB-45 and were reclassified as epithelioid AML; one of the lesions was designated as an unclassified renal tumor; and the final lesion was determined to be an oncocytoma. This study suggests that renal cell carcinoma is less commonly associated with TSC than previously believed. It is also possible that sporadic epithelioid AML have also been misclassified as RCC. Therefore, it is not possible to determine the true incidence of epithelioid AML; however, at our institution, we diagnosed four cases of epithelioid AML during a 17-month period, suggesting that epithelioid AML are not uncommon.

Our study raises two important clinical considerations.

First, The diagnosis of epithelioid AML should be considered in patients diagnosed with conventional RCC with predominantly sarcomatoid features, especially if patients have clinical stigmata of TSC. The diagnosis can be established by identifying epithelioid cells within the tumor, and staining for melanoma markers such as HMB-45 and melan-A, and smooth muscle cell markers such as HHF-35, SMA and caldesmon. The diagnosis can be further validated by confirming the absence of staining for epithelial markers, which are found in RCC but not AML.

For patients with metastatic or recurrent renal cancer, accurate diagnosis allows for proper selection of systemic therapies. Conventional RCC is resistant to standard chemotherapies and is best treated with cytokine-based therapies and small molecule tyrosine kinase inhibitors. However, epithelioid AML are part of the perivascular epithelioid cell tumor (PEComa) family of tumors, which include clear cell ‘sugar’ tumors of the lung and lymphangioleiomyomas. These lesions are considered chemosensitive. Epithelioid AML have been reported to respond to doxorubicin. In other reports, systemic treatments have included dacarbazine, ifosfamide, cyclophosphamide and cisplatin.

Second, all tumors in our study were devoid of fatty elements on CT scan. We were not able to find any reports of epithelioid AML with fat densities noted on CT or magnetic resonance imaging (MRI). Therefore, there is no evidence to recommend more aggressive surgical management for renal lesions seen on abdominal imaging with discrete fat densities. These lesions should be considered conventional AML with benign clinical behavior.

However, it is important to recognize that epithelioid AML can develop adjacent to conventional AML or even within a conventional AML. In our second case, a patient with TSC had multiple conventional AML noted on CT. She also had a single renal mass devoid of fat densities, which was surgically resected and confirmed to be an epithelioid AML. VanderBrink et al. reported an epithelioid AML that developed within a conventional AML. Their report includes a CT scan showing an enhancing renal mass surrounded on all sides by fat densities representing a conventional AML.

Fig. 1  Computed tomography (CT) scan showing a 13-cm right renal mass (case 1) with extension into the inferior vena cava. The tumor thrombus extended to the level of the hepatic veins.

Fig. 2  CT scan of a patient with tuberous sclerosis complex (TSC; case 2). (a) Enhancing left renal mass devoid of fat densities and considered suspicious for renal cell carcinoma. (b) Multiple, bilateral renal lesions characteristic of conventional angiomyolipomas.
Epithelioid angiomyolipoma (AML) is distinguished from conventional AML by presence of large epithelioid cells, which have abundant eosinophilic cytoplasm (HE stain, original magnification ×100). Neoplastic cells show strong cytoplasmic granular immunoreactivity to HMB-45 (immunohistochemical stain with HMB-45, original magnification ×100). Neoplastic cells show strong cytoplasmic immunoreactivity to melan-A (immunohistochemical stain with melan-A, original magnification ×100). Neoplastic cells show strong cytoplasmic immunoreactivity to SMA (immunohistochemical stain with SMA, original magnification ×100). All from case 4.

**Table 3**: Reports of metastatic AML

| Age/sex | TSC | Indication for nephrectomy | Size of renal mass (cm) | HMB-45 | Necrosis | Mitoses | Follow up (months) | Metastases | Sites of metastases |
|---------|-----|-----------------------------|-------------------------|--------|----------|---------|-------------------|------------|-------------------|
| Al-Saleem 21/F | + | Suspected RCC | NA | + | Yes | Yes | Lung, liver | DOD (3) | Lung, liver |
| Ferry 49/F | – | NA | 15 | + | Yes | Yes | Lung | DOD (5.5) | Lung |
| Christiano 42/M | – | Suspected RCC | 20.5† | + | Yes | Yes | Lung | AWD (15) | Lung |
| L’Hostis 72/F | – | NA | 9 | + | NA | Yes | Liver, perivertebral | DOD (24) | Liver, perivertebral |
| Pea (case 3) 24/F | + | Hemorrhage | NA | + | Yes | No | Pelvis, liver | DOD (12) | Pelvis, liver |
| Pea (case 4) 29/M | + | Suspected RCC | NA | + | NA | Yes | Lungs, liver | DOD (18) | Lungs, liver |
| Cibas 49/M | – | NA | NA | + | Yes | Yes | Liver | AWD (6) | Liver |
| Yip 75/M | – | Suspected RCC | 20 | + | Yes | NA | Liver, retroperitoneum | DWD (9) | Liver, retroperitoneum |
| Ong 74/F | – | Suspected RCC | 9 | + | Yes | NA | Adrenal | OVD (9) | Adrenal |
| Martignol 50/M | – | Suspected RCC | 6 | + | No | Yes | Lung, abdomen, pelvis | AWD (120) | Lung, abdomen, pelvis |
| Current study 69/M | – | Suspected RCC | 13† | + | Yes | Yes | Liver, peritoneum | AWD (10) | Liver, peritoneum |
| Current study 46/F | – | Suspected RCC | 17 | + | No | Yes | Liver, lymph nodes | AWD (16) | Liver, lymph nodes |

IVC thrombus. NA, not available; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease following surgery/treatment.
Conclusion

Epithelioid AML are capable of aggressive clinical behavior. They may occur sporadically or as part of the TSC. Histologically, they may resemble conventional RCC and melanoma, and can be distinguished by staining for HMB-45 and identifying epithelioid cells within the tumor. On CT scan, epithelioid AML appear as enhancing lesions devoid of fat densities.

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