

Clinical evaluation of epithelioid angiomyolipoma



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Antonino Graziano, Marco Santangelo, Danilo Savio Umana

Department of Surgery, University of Catania, Catania, Italy

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OBJECTIVE: *Epithelioid angiomyolipomas (AML) of the kidney are malignant tumors with aggressive clinical behavior. Methods The Authors report on some cases epithelioid AM recently diagnosed at their Institute to highlight the spectrum of clinical presentations.*

RESULTS: *In all cases, renal lesions observed at computed tomography were suspicious for renal cell carcinoma (RCC). Histologically, these tumors can 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.*

Four 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.

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 metastasized.

KEY WORDS: Angiomyolipoma, Epithelioid angiomyolipoma, Kidney, Renal cell carcinoma.

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 are 2.0-6.4% of all renal tumors; however, they represent one of the most common benign renal lesions of the kidney¹⁻³. AML can occur as an isolated renal lesion or as apart 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 RCC⁶. 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

From June 2000 to November 2004, four patients were diagnosed with AML at our Institution. According with institutional review 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 I).

Immunohistochemical analysis was performed using appropriate positive and negative controls. Formalin-fixed, paraffin-embedded samples were stained by immunohistochemistry using avidin-biotin-peroxidase complex.

TABLE I - *Antibodies used for immunohistochemistry.*

Cytokeratin Monoclonal
Muscle actin Monoclonal
Caldesmon Monoclonal
SMA, smooth muscle actin.

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For correspondence: Prof. Antonino Graziano, University of Catania, Department of Surgeru, Via S. Sofia 86, 95125 Catania (e-mail: graziano@policlinico.unict.it).

Results

Table II 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. Four 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). Ten months after the surgical resection of AML, the patient had recurrence in the liver and peritoneum. One renal lesion measured 6 cm and did not contain fat (Fig. 2a,b). Following partial nephrectomy, the histology was AML. The specimen contained adjacent lesions consistent with conventional AML containing vascular, smooth muscle and mature adipose elements. The third patient had AML diagnosed after undergoing a laparoscopic partial

TABLE II - Patients diagnosed with epithelioid angiomyolipoma (AML).

Age (years)	69-37
Sex	Male Female
Renal lesion Symptomatic	Size (cm) 13- 4
Fat densities (CT finding)	No
Tumor thrombus	Necrosis Yes
TNM stage	T3bN0M0‡ T1aN0M0
Immunohistochemistry	HMB-45 Positive
Melanin	Positive
Time to recurrence/ (months)	8/16
Recurrence	Liver, peritoneum, Lymph nodes
Status	Alive
Extension into perinephric fat and extension into the inferior vena cava to the level of the hepatic veins.	
TSC, tuberous sclerosis complex.	

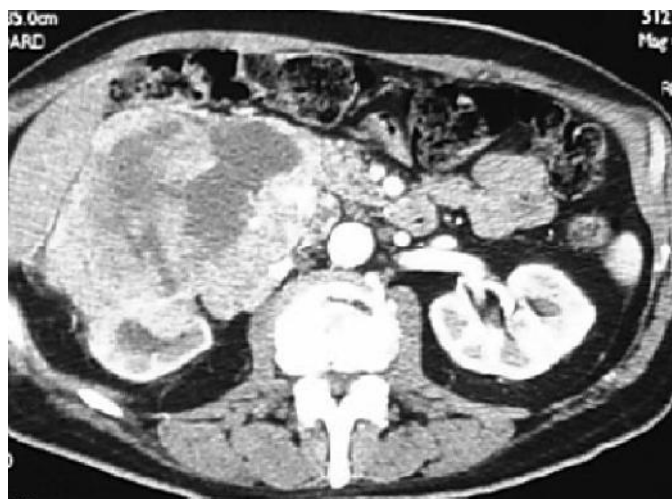


Fig. 1 - Computed tomography (CT) scan showing a 13-cm right renal mass with extension into the inferior vena cava. The tumor thrombus extended to the level of the hepatic veins

nephrectomy for an incidentally noted 1.8-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 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. 2a-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. 2d), HHF-35 and caldesmon.

Discussion

AML have been considered benign lesions that can be diagnosed radiographically in the kidney are generally nephrectomy or angiographic embolization has been recommended for symptomatic lesions and lesions greater than 4 cm.^{9,10} Most asymptomatic lesions are followed with interval abdominal imaging. However, 8 cases of metastatic AML have been reported, 2, 6, 11-17 and our study includes two additional cases of metastatic AML.

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.⁷ These tumors may also be focally positive for smooth muscle markers such as SMA.¹⁸ 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.

Our study raises two important clinical considerations: 1) diagnosis of epithelioid AML should be considered in patients diagnosed with conventional RCC with pre-

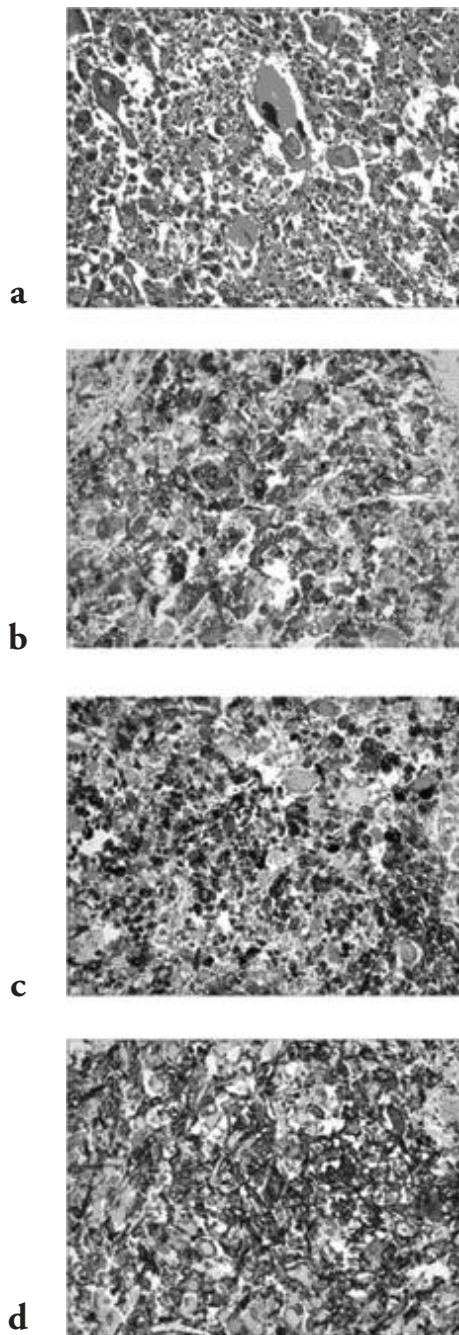


Fig. 2 - (a) Epithelioid angiomyolipoma (AML) is distinguished from conventional AML by presence of large epithelioid cells, which have abundant eosinophilic cytoplasm (HE stain). (b) Neoplastic cells show strong cytoplasmic granular immunoreactivity to HMB-45 (immunohistochemical stain with HMB-45). (c) Neoplastic cells show strong cytoplasmic immunoreactivity to melan-A (immunohistochemical stain with melan-A). (d) Neoplastic cells show strong cytoplasmic immunoreactivity to SMA (immunohistochemical stain with SMA)

dominantly 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, and smooth muscle and caldesmon. The diagnosis can be further validated by confirming the absence of staining for epithe-

lial 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 doxorubicin.¹³ In other reports, systemic treatments have included dacarbazine, ifosfamide, cyclophosphamide and cisplatin^{14,19}. These lesions are considered chemosensitive. The AML have been reported to respond; .2) Our study 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, here 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.¹³ She also had a single renal mass devoid of fat densities, which was surgically resected and confirmed to be an AML:

VanderBrink et al. reported an epithelioid AML that developed in a conventional AML²⁰. Their report includes a CT scan showing an enhancing renal mass surrounded on all sides by fat densities presenting a conventional AML.

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.

Riassunto

OBIETTIVO: Gli angiomyolipomi del rene sono tumori maligni con comportamento clinico aggressivo.

METODI: Viene riportata una rassegna si riporta una recente di casi con AML diagnosticati nella nostra istituzione al fine di evidenziare lo spettro di presentazioni cliniche.

RISULTATI: In tutti i casi trattati, le lesioni renali osservate con la tomografia computerizzata erano orientate per carcinoma renale.

Istologicamente questi tumori possono assomigliare a RCC. La diagnosi di angiomyolipoma è stata stabilita da una chiazatura positiva per melanoma e presenza di cellule epitelioidi. Quattro pazienti presentavano un tumore renale che si estendeva alla vena cava inferiore al livello delle vene epatiche. Due pazienti svilupparono ricor-

rente malattia metastatica successiva a nefrectomia.

CONCLUSIONI: Questi tumori sono distinti da RCC da immunostaining positivo per marcatori di melanoma.

La loro somiglianza a RCC convenzionale su imaging TC viene differenziata dalla clinica in quanto l'AML epitelioide può essere localmente aggressivo e metastatizzante.

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