Angiomyolipoma of the kidney: Clinicopathological and immunohistochemical study

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Abstract

Overview: Although angiomyolipoma (AML) is a relatively rare entity, it is the most common benign mesenchymal neoplasm of the kidney.

The aim of this study: To highlight the clinicopathological characteristics of AML and to assess the role of Human Melanoma Black-45 (HMB-45), Melan-A, smooth muscle actin (SMA), S-100 and cytokeratin in its diagnosis.

Materials and methods: The study included 15 cases of AML. Clinical and radiological data were retrieved from the archival files and all cases were subjected to a histopathological evaluation as well as immunohistochemical staining for HMB-45, Melan-A, SMA, S-100, and cytokeratin.

Results: AML was more common in females (female: male = 4:1), the mean age was 53.9 ± 6.45 years. 60% of patients were symptomatic while the remaining 40% were asymptomatic. A statistically significant relationship was found between size of the tumor and the presence of the symptoms (P = 0.02). Patients with tumor size less than 4 cm were asymptomatic, while those with tumor size larger than 4 cm had different symptoms.

Thirteen cases were classic AML, while 2 cases were epithelioid AML. Classic AML demonstrated admixture of fatty tissue, thick-walled blood vessels, and smooth muscle, while epithelioid AML...
Introduction

Angiomyolipoma belongs to a family of neoplasms called perivascular epithelioid cell tumors (PEComas) [1–8]. The World Health Organization (WHO) defines PEComas as “mesenchymal tumors composed of histologically, ultrastructurally, and immunohistochemically distinctive perivascular epithelioid cells C [9]. PEComas are a family of related mesenchymal neoplasms that include angiomyolipoma (renal and extrarenal variants), lymphangiomyomatosis, clear cell ‘sugar’ tumor of the lung, clear cell myomelanocytic tumor (CCSMT) of the fallopian ligament/ligamentum teres, primary extrapulmonary ‘sugar’ tumor and clear cell tumors of diverse sites [10–17].

All these tumors share a distinctive cell type, the perivascular epithelioid cell or ‘PEC’ (which has no known normal tissue counterpart). The perivascular epithelioid cell (PEC) is a “novel” cell type showing morphologic, immunohistochemical, ultrastructural, and genetic distinctive features, such as an epithelioid appearance with a clear to granular cytoplasm, a round to oval, centrally located nucleus and an inconspicuous nucleolus, and a typical perivascular location [11–16]. Immunohistochemically, PEC expresses myogenic and melanocytic markers, such as HMB-45, Melan-A/Mart1, smooth muscle actin and, less commonly, desmin [18,19].

HMB-45 is a monoclonal antibody that reacts against an antigen present in melanocytic tumors and stands for Human Melanoma Black. The specific antigen recognized by HMB-45 is now known as Pmel 17.

HMB-45 is nonreactive with almost all non-melanoma human malignancies, with the exception of rare tumors showing evidence of melanogenesis (e.g., pigmented schwannoma, clear cell sarcoma, and PEComas) [20].

The Melan-A gene, also known as MART-1 (Melanoma Antigen recognized by T-cells), was cloned from a melanoma cell line. Two monoclonal antibodies have been raised; A103 and M2-7C10. A103 has been the most extensively studied in AML (100%), Melan-A was positive in 13/15 (87%) while SMA was positive in 11/15 (73%) of AML with variable staining intensity. All cases of AML were negative for S-100 and cytokeratin.

Conclusion: AMLs have characteristic clinicopathological and immunohistochemical features and their recognition is crucial for proper diagnosis and treatment.

Materials and methods

A total of 15 cases of AML were studied in this work. 13 cases were obtained retrospectively, from the archives of the Department of Pathology, Faculty of Medicine, Tanta University during the period between 2000 and 2012, while 2 cases (cases number 7 and 8) were selected from the wards of the internal medicine department, Tanta University hospital during the period between October 2011 and January 2013. The two cases were admitted for treatment of anemia caused by frank hematuria; and they were subjected to the following: informed written consent, thorough history taking, clinical examination both general and local, routine laboratory investigations;
complete blood picture, liver and kidney function tests, fasting and 2 h postprandial blood glucose, complete lipid profile. Imaging studies: abdominal ultrasound, abdominal CT and abdominal MRI if needed.

All available clinical data for each case including age, gender, symptoms, type of the surgical procedure, radiological findings, and tumor size, were obtained from the accompanying clinical sheets. Paraffin blocks were obtained and sectioned. The slides were stained with H&E to confirm the histological diagnosis.

**Classification of AMLs**

In this study, AMLs were classified as classic and epithelioid according to the 2004 World Health Organization classification of tumors [9]. Classic AMLs were diagnosed when the tumor is composed of a variable proportion of adipose tissue, smooth muscle cells, and abnormal thick-walled blood vessels and all 3 components were readily identified. While epithelioid AMLs (EAMLs) were diagnosed when the tumors show proliferation of predominantly epithelioid cells.

**Pathological parameters**

Tumor size was recorded according to the largest tumor diameter either by radiological findings or by gross examination. The percentage of adipose tissue, smooth muscle, blood vessels, and epithelioid components was recorded for all cases of AML.

The following pathological parameters were also evaluated: tumor necrosis, hemorrhage, lymphovascular, and perineural invasion.

**Immunohistochemistry**

Immunohistochemical assays were performed using the following antibodies: HMB-45, Melan-A, smooth muscle actin, S-100, and cytokeratin. The details of primary antibodies are summarized in Table 1.

For immunohistochemical staining 4 µm paraffin tissue sections were deparaffinized in xylene and rehydrated in descending ethanol concentrations to distilled water. Subsequently, antigen retrieval in the tissue sections was achieved by placing them in a Coplin jar filled with 0.01 M citrate buffer, pH 6.0, and boiling for 5 min in a microwave oven at 600 W. The sections were then cooled to room temperature, equilibrated in phosphate buffer solution (PBS), pH 7.4, for 10 min and treated with 0.3% H₂O₂ in methanol to block endogenous peroxidase activity. Nonspecific antibody binding sites were blocked by 30 min of incubation with normal mouse serum. The primary antibodies were applied for 2 h at room temperature. Secondary goat anti-mouse antibody (Labvision) and streptavidin–biotin–peroxidase complex were used, each for 1 h. The sections were washed thoroughly in PBS after each antibody incubation. Peroxidase activity was detected using 0.05% diaminobenzidine containing 0.01% H₂O₂ and counterstaining with hematoxylin. Negative controls obtained by the use of non-immune normal mouse serum as the primary antibody. Positive controls consisted of sections from malignant melanoma (HMB-45 and Melan-A), leiomyoma (smooth muscle actin), and normal human tonsil (cytokeratin).

**Scoring methods**

The staining for all markers was scored as strong (3), moderate (2), weak (1), or negative (0). Cytoplasmic staining was scored as positive for HMB-45, Melan-A, smooth muscle actin, and cytokeratin; while nuclear staining was considered positive for S-100.

**Statistical analysis**

Qualitative data were presented as number and percentage. Chi-square was used to test the relation between the presence or absence of symptoms and tumor size. Quantitative data were presented as mean and standard deviation. *P* value below 0.05 was considered statistically significant. All analyses were performed using SPSS statistical software (SPSS V.16, Inc., Chicago, IL).

**Results**

A total of 15 cases of AML were studied in this work, 13 cases were diagnosed as classic AML while 2 cases were epithelioid AML (cases 14 and 15).

The clinicopathological parameters in AML cases were listed in Table 2.

**Clinical data**

Twelve patients were females while the remaining 3 cases were males; female: male ratio was 4:1. The age of the patients ranged from 43 to 64 years with a mean age of 53.9 ± 6.45 years.

In this work, 9 cases (60%) were symptomatic; some patients presented by more than one symptom, while the remaining 6 patients (40%) were asymptomatic and were identified incidentally during medical examinations for other diseases (Table 3). None of the patients had a history of tuberous sclerosis.

There was a statistically significant relationship between size of the tumor and the presence of the symptoms (*P* = 0.02). 6 patients (40%) with tumor size less than 4 cm (2.68 ± 0.78 cm) were asymptomatic, while the remaining 9 patients with tumor size larger than 4 cm (4.71 ± 0.9 cm) had different symptoms.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of antibodies used for evaluation.</th>
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<tr>
<td><strong>Antibody</strong></td>
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<tr>
<td>Melanoma</td>
<td>Monoclonal HMB 45</td>
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<td>Melan A</td>
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U/S, ultrasound; CT, computed tomography; MRI, Magnetic Resonance Imaging; CECT, contrast-enhanced CT; Rt., right; Lt., left.
The patients were subjected to different procedures that were listed in Table 4. Three patients (cases 7, 8, and 14) underwent arterial embolization to prevent hemorrhagic complications.

The imaging techniques performed to the patients are summarized in Table 5. There were two patients who had no radiological records (cases 12 and 13).

**Classic AML**

Ultrasonic examination revealed well circumscribed echogenic masses.

The plain CT scan showed well-marginated heterogeneous tumors with predominantly fatty attenuation with negative CT number. The average attenuation depended on the relative proportions of fat and other soft tissue in the angiomyolipoma. Both contrast-enhanced CT and MRI were performed in case number (6) which was multifocal and bilateral. Contrast-enhanced CT showed well circumscribed hypodense lesions in both kidneys displaying fat density with the largest one in left kidney measuring 32.8 × 32.6 mm (Figure 1). Similarly, MRI confirmed CT findings and showed high signal intensity focal lesions in the cortex of both kidneys (Figure 2).

The characteristic appearances of angiomyolipomas with MRI include variable areas of high signal intensity within the tumor on both T1-weighted and T2-weighted images. On a non-enhanced T1-weighted image, high signal intensity is present because of the fat content. On T2-weighted images, the signal remains iso-intense relative to that of perinephric fat.

**Epithelioid AML**

CT of both cases of epithelioid AML showed isolated heterogeneous renal masses devoid of fat densities. MRI supported the CT findings and both cases were considered suspicious for renal cell carcinoma.

**Pathological findings**

**Classic AML (13 cases)**

The mean size of all AML cases was 3.9 ± 1.32 cm; the mean size of classic AML was 3.6 ± 1.14 cm (range 1.2–6 cm).
was multifocal within the right kidney; the largest mass was 4 cm as measured by CT.

Gross pathology
The tumors showed non-infiltrative, well-circumscribed and non-encapsulated soft tissue masses. The cut surfaces of tumors were yellow brown or dark brown according to the percentage of the 3 components. All cases showed no hemorrhage or necrosis.

Microscopic examination
At scanning magnification, the lesions were well circumscribed in all cases (Figure 3).

AML was composed of an admixture of blood vessels, smooth muscle, and mature adipose tissue, the latter forming vascular cuffing around blood vessels (100x). The tumors showed non-infiltrative, well-circumscribed and non-encapsulated soft tissue masses. The cut surfaces of tumors were yellow brown or dark brown according to the percentage of the 3 components. All cases showed no hemorrhage or necrosis.

Microscopic examination
At scanning magnification, the lesions were well circumscribed in all cases (Figure 3).

AML was composed of an admixture of blood vessels, smooth muscle, and mature adipose tissue, the latter forming vascular cuffing around blood vessels (100x).

No necrosis was detected; however, hemorrhage was seen in 2 cases (15.4%) (cases 7 and 8). There were no vascular or perineural invasion.

Epithelioid AML (2 cases)
Both cases were in the right kidney. Case (14) was subjected to CT guided needle biopsy followed by arterial embolization and measured 5.4 cm. Case (15) underwent radical nephrectomy. It measured 5.6 cm and its cut surface was brown and friable with focal necrosis and hemorrhage.

At scanning magnification, case (15) appeared infiltrative with irregular edges.

Both cases demonstrated proliferation of predominantly epithelioid cells with abundant granular cytoplasm arranged around thick walled blood vessels. No fatty tissue was seen. The tumor cells had enlarged vesicular nuclei and prominent nucleoli with focal nuclear atypia (Figure 5) and mitotic figures [one mitotic figure per 10 high power field (HPF)].

Focally, the cells had a nested, trabecular, or sheet-like growth pattern.

Both cases showed hemorrhage. Case (15) also showed areas of necrosis, there were no vascular or perineural invasion.

Immunohistochemistry
The detailed immunohistochemical characteristics that were observed in AMLs using HMB-45, Melan-A, SMA, S-100 and cytokeratin are summarized in Table 6.

HMB-45 was positive in all cases of AML (100%), Melan-A was positive in 13/15 (87%) while SMA was positive in 11/15 (73%) of Figure 6.
S-100 and cytokeratin were done to exclude melanoma and renal cell carcinoma and all cases were negative for both markers.

All 13 cases of classic AML (100%) showed positive cytoplasmic immunoreactivity for HMB-45 while 11/13 cases (85%) were positive for Melan-A. SMA was positive in 10/13 (77%) of cases.

Both cases of epithelioid AML exhibited strong staining for HMB-45 and Melan-A. One case was negative for SMA, while the second case demonstrated weak staining for SMA.

Discussion

Classic renal angiomyolipoma is one of the most common benign renal lesions of the kidney, comprising 2.0–6.4% of all renal tumors and approximately 1% of surgically removed renal tumors. [9,34,35].

Epidemiologically, AML has a distinct female predominance, as observed in our study (female: male = 4:1). This finding was consistent with previously published studies [5,9]. However, Yang et al. [1] reported that female: male ratio was 2:1.

The patients were in the fourth to sixth decades of life, with a mean age of 53.9 ± 6.45 years. Concomitant finding was previously reported [1,5,9]. Martignoni et al. stated that the mean age at diagnosis of AML in surgical series is between 45 and 55 for patients without TS [9].

60% of AML cases in this study were symptomatic. The clinical manifestations included hematuria (33%), anemia (26.7%), hypertension (20%), and flank pain (13%). A similar finding was previously reported by Pode et al. [36], Yamakado el al. [37], and Soorakumaran et al. [38]. The former authors also found that the most severe symptoms were associated with rupture of the tumor and mentioned that patients with ruptured angiomyolipoma often present acutely with pain as a result of hemorrhage and up to 20% are in shock at the time of initial presentation, while Yamakado et al. [37] reported that there are significant relationships between tumor size and rupture in angiomyolipomas and added that tumor size is the main predictor of hemorrhage.

In this work, we found a statistically significant relationship between the size of the tumor and the presence of the symptoms ($P = 0.02$). Patients with tumor size more than 4 cm tended to be symptomatic, while those with tumor size less than 4 cm were asymptomatic. These results confirm those previously reported by Dickinson et al. [39].

In our current study, renal AMLs had clearly defined radiological characteristics. Classic AML by ultrasound appeared as a well-defined echogenic lesion. Similar finding was previously documented by Siegel et al. [40] who also mentioned that renal angiomyolipomas are intensely echogenic masses and a reduction of echogenicity in AMLs is related to a decrease in the quantity of fat and/or an increase in the amount of myogenic components.

In this work, unenhanced CT demonstrated the presence of fat in classic AML. Fat appeared as hypodense tissue. These results were concomitant with those of Halpenny et al. [41], who further concluded that attenuations of less than –20 Hounsfield units (HU) are widely accepted as confirming the presence of fat and this finding virtually confirms the diagnosis of angiomyolipoma.
Both cases of epithelioid AML in this study contained no fat in CT and MRI and therefore, RCC was suspected. This finding confirms and extends those previously reported by Varma et al. [8], Tsai et al. [35], and Lane et al. [42]. On the contrary, it is contradicted with that of Chen et al. [43] who reported a case of aggressive epithelioid AML which showed fat by both CT and MRI.

It is sometimes difficult to differentiate AML with minimal fat from RCC. Kim et al. [44] identified some CT scan findings valuable for differentiating angiomyolipoma with minimal fat from renal cell carcinoma including homogeneous tumor enhancement, prolonged enhancement pattern, and high tumor attenuation on unenhanced scans in AMLs.

None of the patients in this study had a history of TSC. AMLs in patients with TSC have no sex predilection, in the third and fourth decades of life, they are usually asymptomatic, usually bilateral, small and multifocal. Sporadic AMLs occur in older patients, with a female predominance; they are single, unilateral and larger than those associated with TSC [7].

All but 2 cases of classic AML (11/13, 85%) in this work were unilateral and solitary. Whereas the other 2 cases of classic AML were multifocal, and one of them was bilateral. Both cases showed the typical triphasic pattern. This finding is in keeping with those of Varma et al. [8], who also stated that classic renal angiomyolipomas may have locoregional or multicentric involvement; however, these lesions have always behaved in a benign manner and have not been associated with an adverse prognosis. Similarly, Yang et al. [1] in their study found that 6/122 of the classic renal AML cases presented with multiple foci. Two of the cases had foci located in the bilateral kidney as well. Moreover, Brimo et al. [45] reported that classic AML is considered to be benign even in the presence of vascular or regional lymph node involvement, which is regarded as indicative of multifocal growth, rather than aggressive behavior.

In this work, all cases of classic AML were positive for HMB-45 (100%), Melan-A was positive in 85% of cases, while SMA was positive in 73%. All classic AML cases were negative for S-100 and cytokeratin. Similar results have been reported by most, but not all other investigators [1,4-9]. Kim et al. [46], on the other hand, reported that S-100 was positive in 8/10 classic AML cases. However, this variation could be attributed to the use of different antibody clones in their study.

Two cases in this study were diagnosed as an epithelioid angiomyolipoma. The tumors were composed mainly of epithelioid cells with focal nuclear pleomorphism, prominent nucleoli, and mitoses. No fatty tissue was identified. Necrosis was seen in one case, while hemorrhage was present in both cases. Both cases showed strong cytoplasmic staining for HMB-45 and Melan-A. SMA was negative in one case and weakly positive in the second one. Both cases were negative for S-100 and cytokeratin. Similar findings were documented by Varma et al. [8], Tsai et al. [35], and Aydin et al. [47]. On the contrary; Yang et al. [1] reported strong SMA and actin in epithelioid AML and moderate HMB-45 staining.

Varma et al. [8] and Tsai et al. [35] mentioned that epithelioid AML can resemble sarcomatoid RCC and metastatic melanoma, therefore, the final diagnosis is established based on the presence of positive reaction for HMB-45, Melan-A and SMA and negative reaction for S-100 and cytokeratin.

The epithelioid variant of renal angiomyolipoma is a recently described entity that has been recognized in the 2004 WHO classification of renal tumors and shows a high degree of association with tuberous sclerosis, and demonstrates aggressive behavior unlike classic renal angiomyolipomas, which are commonly benign [48].

In otherwise classic AML, areas of epithelioid cells can be observed, raising the question how much of these epithelioid cells should be present to call a tumor “epithelioid angiomyolipoma”. There is no definite cut off point for the exact amount of epithelioid cells that should be present. Lane et al. [42] proposed that more than 95% of the tumor should contain epithelioid cells to call it epithelioid AML, while Yang et al. [1] reported that the epithelioid component in their study accounted for 90% of the tumor. On the other hand, the WHO states that “epithelioid AML is a potentially malignant mesenchymal neoplasm characterized by proliferation of predominantly epithelioid cells”, however, the extent of the epithelioid component that warrants the designation of a tumor as epithelioid AML has not been established [48].

Therefore, Martignoni et al. suggested a consensus meeting to address this issue [7]. Martignoni et al. [49] first described the epithelioid variant of renal angiomyolipoma in 1994. The authors described 7 cases of renal tumors composed of sheets of bizarre oxyphilic epithelioid cells, having large nuclei with prominent nucleoli, uniformly positive for HMB-45, focally positive for actin and negative for keratin and epithelial membrane antigen.

Prior to the identification of this variant, many cases were misdiagnosed as renal cell carcinomas. Pea et al. [50] reexamined the tissue paraffin blocks and slides from 5 different cases of tuberous sclerosis-associated renal cell carcinomas and reclassified 3 cases as “epithelioid variant of angiomyolipoma,” based on HMB-45 immunoreactivity and negative cytokeratin immunostaining and the authors suggested that the increased incidence of RCC associated with TSC may be due to incorrect classification of EAML as RCC.

Approximately 30% of epithelioid AMLs (EAMLs) have malignant potential [35]. Therefore, in 2010, Brimo et al. [45] proposed the concept of atypical EAMLs, and suggested that certain atypical morphological features may be correlated with malignant behavior. Those features include: more than 70% atypical epithelioid cells; more than 2 mitotic figures per 10 HPF; atypical mitotic figures; and necrosis. Additionally, these authors concluded that the presence of three or more of the above features predicts an increased risk of clinically malignant behavior. In our study, the percentage of atypical epithelioid cells were much lower than 70%, the mitotic count was less than 2/10 HPF, and there was no abnormal mitotic figures. Only one case showed necrosis. Based on these criteria, the 2 cases of epithelioid AML in this work do not qualify as atypical epithelioid AML.

Tsai et al. [35] mentioned that the diagnosis of AML can sometimes be established by imaging alone, but CT-guided percutaneous biopsy (2–5 cores) is sometimes necessary if no fat is detected and RCC is suspected as in case no. 14 in this work.

The management of renal AMLs is widely discussed in the literature [8,31,35,42,51,52] and is primarily based on clinical presentation, the size of the tumor, bilaterality, and malignant potential. Thus, in asymptomatic tumors, evaluation with abdominal ultrasound and/or CT-scan every six or twelve months, depending on the size of the tumor, greater or less than 4 cm, respectively, is necessary. In symptomatic and/or
bilateral tumors, artery embolization, selective kidney or conservative surgery (nephron sparing) are the treatments of choice. Radical nephrectomy is reserved for those cases with hemodynamic instability due to massive bleeding, large tumors, or if RCC is suspected [42].

Because approximately one third of cases of EAML show advanced disease, it is essential to initiate appropriate treatment with close follow-up, as for RCC, owing to its malignant potential [35].

Currently, there is no known effective therapy for epithelioid angiomyolipoma other than surgery [8]. Metastatic EAML has been treated with a variety of chemotherapeutic agents including doxorubicin, dacarbazine, ifosfamide, cyclophosphamide and cisplatin [51]. As mentioned earlier, Kenerson et al. [31] found that epithelioid angiomyolipomas uniformly exhibit activation of the mTOR cascade, which contributes to the tumor growth and progression. This suggests the possibility that mTOR inhibitors, such as rapamycin or temsirolimus, may provide therapeutic benefit in the treatment of epithelioid angiomyolipomas. A study by Ramon et al. using selective arterial embolization showed promising results especially in prevention of hemorrhagic complications of renal angiomyolipomas and possible preservation of renal function [52].

Conclusion

Renal angiomyolipoma is an uncommon benign tumor, which may represent a challenge for clinical and pathological diagnosis. Symptomatic tumors are usually 4 cm or more. The presence of fat is highly suggestive of classic AML by CT; on the other hand, epithelioid AML contains no fat in CT and therefore may be misdiagnosed as RCC. AMLs are characteristically positive for HMB-45, Melan-A, and SMA and negative for S-100 and cytokeratin.

Conflict of interest

The authors declare no financial relationships with any industry through employment, consultancies, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit either directly or through immediate family.

References


