Original Article

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Renal Angiomyolipoma: A Clinicopathological Study of Seven Cases and Review of the Literature

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Abstract

Objective: Renal angiomyolipomas (AMLs) are mesenchymal kidney tumours that have triphasic histology. This study aimed to present the clinical, pathological and immunohistochemical features of seven AML cases along with a review of the relevant literature.

Materials and Methods: Seven cases of pathologically diagnosed AML were included in the study. The presence of fat tissues, smooth muscle cells, blood vessels and epithelioid components were determined for all cases. Tumour necrosis, haemorrhage, mitosis, lymphovascular and perineural invasion were also recorded. Immune markers [human melanoma black-45 (HMB45), Melan-A, smooth muscle actin (SMA), cytokeratin], previously applied to the tissue sections, were re-evaluated as positive and negative staining.

Results: All cases were classic AML types. Five patients had flank pain and two had haematuria. The tumour was located in the left kidney in two cases and in the right kidney in five cases. The mean size of the AMLs was 7.36±4.23 cm. Tumours were separated from the normal kidney parenchyma with good margins and composed of mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells in varying proportions. Immunohistochemically, all cases were positive with HMB-45, Melan-A and SMA. No case was positive for cytokeratin staining.

Conclusion: Correct histological diagnosis of renal AML subtypes is crucial. Incorrect diagnosis of classic renal AML may lead to inadequate postoperative management. Clinicians should be aware of the malignant potential of epithelioid AML and the need for long-term follow-up.

Keywords: Clinicopathological features, immunohistochemistry, renal angiomyolipoma

Introduction

Renal angiomyolipoma (AML) was first defined in 1951 by Morgan et al. (1). They are mesenchymal kidney tumours containing smooth muscle cells, dysmorphic blood vessels, and adipocytes (triphasic histology). AMLs are usually benign tumours, but at risk of spontaneous bleeding. Generally, AMLs are asymptomatic and found incidentally by routine imaging techniques and rarely become symptomatic (2,3,4).

AMLs are rare kidney tumours and constitute 2%-6.4% of all renal tumours (2). The prevalence of renal AML in the general population ranges from 0.3% to 3%, and female individuals are four times at risk than their male counterparts (5).

The World Health Organization (WHO) identified two types of renal AML: classic AML (CAML) and epithelioid AML (EAML). CAML is a benign tumour and consists of the three components mentioned in the first paragraph. However, EAML has a predominant epithelioid component and potentially malignant behaviour (6). EAML cases were found to present the characteristics of malignancy, such as tumour venous extension, distant metastasis and local recurrence. Therefore, it is important to distinguish EAML from CAML (7).

Approximately 80% of renal AMLs are sporadic and have no association with any Genetic syndrome. However, some AMLs can be seen with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis. Moreover, 10%-20% of renal AMLs are thought to be associated with TSC. In addition, 80%-90% of patients with TSC have AML (8).

The most common group of patients with sporadic renal AMLs are middle-aged women. Generally, sporadic AMLs do not

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cause any symptoms and are detected incidentally during renal imaging. In addition, slow-growing sporadic AML usually does not lead to deterioration of renal function. Some AMLs can grow over time and have increased risk of bleeding in lesions greater than 4 cm (9). Moreover, these tumours can be found outside the kidney, mainly in the retroperitoneal area and in the liver (10). This study aimed to present the clinical, pathological and immunohistochemical features of seven AML cases along with a review of the relevant literature.

Materials and Methods

In this study, 343 patients who underwent radical or partial nephrectomy from 2010 to 2018 at a university hospital were screened retrospectively, and seven patients with pathologically diagnosed AML were included. Clinical information of the patients (age, gender, hospital admission complaints, radiology of tumours, type of surgery) was obtained from medical records.

The study was approved by the University for the non-interventional Clinical Research Ethics Board (approval number: 05, date: 07.03.2019).

Classification of AMLs

AMLs were classified as CAML and EAML according to the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs. CAMLs were diagnosed when the tumour is composed of a variable proportion of adipose tissue, smooth muscle cells and abnormal thick-walled blood cells. When the tumour shows proliferation of predominantly epithelioid cells, the diagnosis was EAML (11).

Pathological Parameters and Immunohistochemistry

The size, localization and focality of the tumours were obtained from the pathology reports. The largest tumour diameter was determined from the macroscopic examination. Presence of fat tissues, smooth muscles, blood vessels and epithelioid components were determined for all cases. In addition, tumour necrosis, haemorrhage, mitosis, extrarenal metastasis and lymphovascular and perineural invasion were recorded. Immune markers [human melanoma black-45 (HMB-45), Melan-A, smooth muscle actin (SMA), cytokeratin], previously applied to tissue sections, were re-evaluated as positive and negative.

Statistical Analysis

The present study has been conducted with 7 patients. The data of the patients were expressed as mean + standard deviation and percentage.

Results

A total of seven CAML cases were analysed in this study. Their clinicopathological features are listed in Table 1. Of the seven patients, five were women (71.4%) and two were men (28.6%), and the female/male ratio was 5/2. The mean patient age was 59±16.7 years, which ranged from 44 to 90 years.

Clinical Features

Five patients (71.4%) had flank pain and two (28.6%) had haematuria. According to the medical records, none of the patients had TSC. Radiologically, four patients (57.1%) had a solid + fatty mass lesion in the renal parenchyma. By radiological examination, one patient (14.3%) had solid tumour, and the tumours of two patients (28.6%) could not be assessed. The patients were subjected to different procedures. Five patients (71.4%) underwent radical nephrectomy, and two patients (28.6%) underwent partial nephrectomy.

Pathological and Immunohistochemical Features

The tumour was located in the left kidney in two cases (28….6 %) and in the right kidney in five cases (71.4%). One patient (14.3%) had multifocal tumour, while other patients had unifocal tumours.

In gross pathology, the mean size of the AMLs was 7.36±4.23 cm (range, 3.5-16 cm). The tumours have marked borders, and the cross sections of the tumours varied from yellow to dark brown according to the percentage of the components they contained. In haematoxylin-eosin staining, tumours were separated from the normal kidney parenchyma with good margins and consisted of mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells (classical triphasic histology) (Figures 1, 2). Blood vessel walls were thick, and some were hyalinised. The mitotic activity was 0-1/10HPF in all tumours. No tumour necrosis, haemorrhage, extrarenal metastasis and lymphovascular and perineural invasion were detected. Immunohistochemically, all cases (100%) were positive with HMB-45 (focal but strong),

Table 1. Clinicopathological features of the cases

Case no	Age	Gender	Symptoms	Radiology	Surgical procedure	Tumour location	Focality	Tumour size (cm)	Diagnosis
1	72	F	Flank pain	Solid mass	Partial nephrectomy	Right	Unifocal	4	CAML
2	44	F	Flank pain	Solid + fatty mass	Radical nephrectomy	Left	Unifocal	5	CAML
3	58	F	Flank pain	NRR	Radical nephrectomy	Left	Unifocal	7	CAML
4	56	F	Haematuria	Solid + fatty mass	Radical nephrectomy	Left	Multifocal	16	CAML
5	90	F	Haematuria	NRR	Radical nephrectomy	Left	Unifocal	3.5	CAML
6	48	M	Flank pain	Solid + fatty mass	Partial nephrectomy	Right	Unifocal	8	CAML
7	45	M	Flank pain	Solid + fatty mass	Radical nephrectomy	Left	Unifocal	8	CAML
Mean	59							7.36	
SD	16.7							4.23	

M: Male, F: Female, NRR: No radiological reports, CAML: Classic type angiomyolipoma, SD: Standard deviation

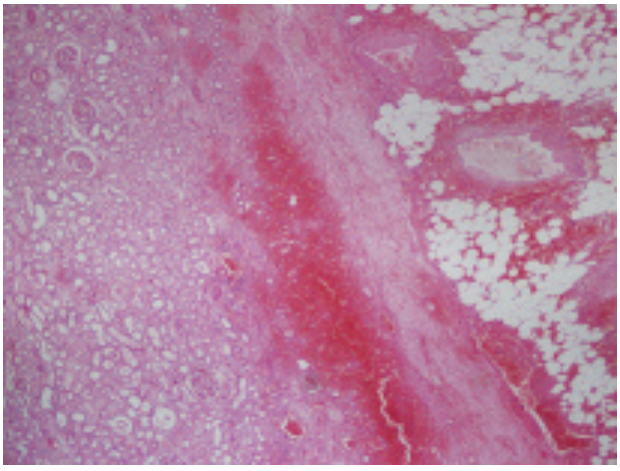

Figure 1. The tumour is separated from the normal kidney parenchyma with good margins (H + E ×40)

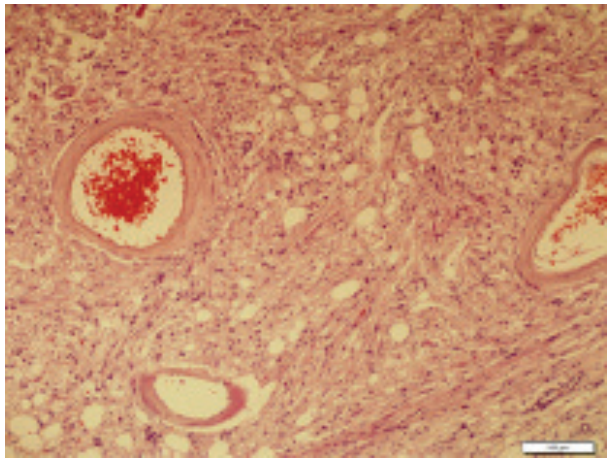

Figure 2. Classic triphasic histology. The tumour is composed of a mixture of mature fat, thick-walled blood vessels, and smooth muscle cells (H + E ×100)

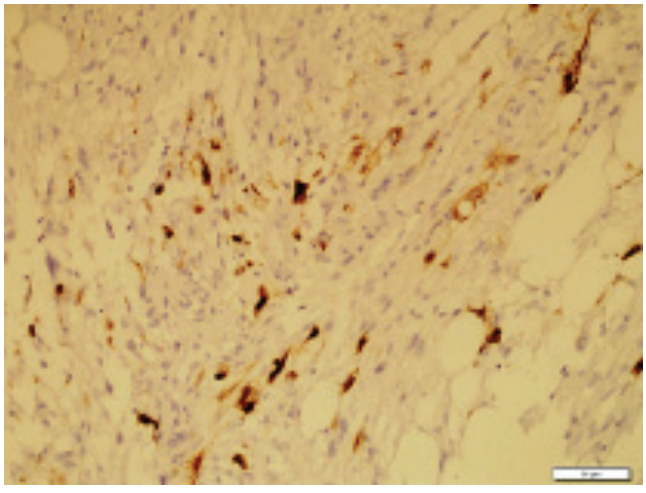

Figure 3. Human melanoma black-45 (HMB-45) expression in tumour cells (HMB-45, ×200)

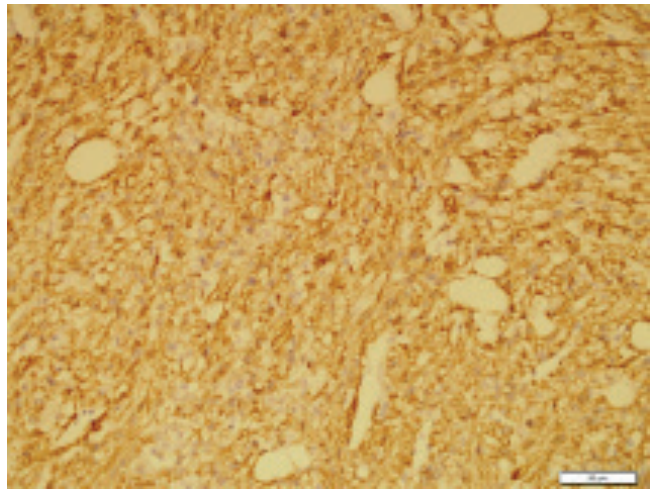

Figure 4. The spindled smooth muscle cells are positive for smooth muscle actin (SMA) (SMA, ×200)

Melan-A and SMA (Figures 3,4). No case was positive for cytokeratin staining.

Discussion

A previous study examined >60,000 patients by abdominal ultrasonography (USG) and reported an AML prevalence of 0.44% (n=270/61,389). In the present study, the occurrence rate of AML was higher in women (0.60%) than in men (0.28%). In addition, 57% of the patients had right kidney and 43% had left kidney involvement (12). Another study examined 1,948 patients by abdominal computed tomography (CT) and reported an AML prevalence of 2.2%, with a mean tumour size of 5 mm (13). Compared with studies performing USG, the high incidence of AML in CT examinations was the result of a more advanced imaging technique of CT and detection of smaller tumours.

In our study, most of the patients (5 of 7 patients) were female, with mean age of 59±16.7 years, which ranged from 44 to 90 years. The tumours were located in the right kidneys in five patients and in the left kidneys in two patients. All cases were unifocal except for one case, which was multifocal. The tumour diameters ranged from 3.5 to 16 cm, with mean diameter of 7.36±4.23 cm. The tumours had good margins, and the cross sections of the tumours varied from yellow to dark brown according to the percentage of the components they contained.

The most serious complications of AML are retroperitoneal haemorrhage (Wunderlich syndrome), haematuria and renal dysfunction. Wunderlich syndrome occurs classically during pregnancy, and haemorrhagic shock may be observed in 20% of the patients (8). Especially, large tumours (>4 cm) may cause complications such as bleeding into the retroperitoneal region or the renal collecting system, even if they are benign (14). AMLs also have the potential to invade local structures. Pregnancy and hormonal treatment are known to increase tumour growth (9). In our study, five patients had flank pain and two had haematuria.

On USG, AML classically present as hyperechoic lesions with posterior acoustic shadowing (8). CT is the most commonly used imaging technique in AML diagnosis, and renal AML diagnosis is established using CT, showing negative fat density (between -10 and -100 Hounsfield units) with an accuracy rate of 86% (4). As the fat content decreases in AML, diagnosis becomes more difficult with CT and USG. Magnetic resonance imaging (MRI) can be used in these cases. A study reported that half of AML cases had poor fat content, thus causing difficulty in differentiating AML from other renal lesions by imaging methods (15). In both T1 and T2 weighted sequences, hyperintense appearance due to fat content and hypointense appearance in fat-suppressed T1 images are helpful in differentiating AMLs from other lesions (16). If the AML cannot be diagnosed with imaging techniques, imaging assisted percutaneous needle biopsy may be recommended as an alternative to surgical exploration. The risk of bleeding after biopsy of AMLs with low fat is not higher than the risk of bleeding of other renal tumours when an appropriate needle is used for biopsy (17).

In the differential diagnosis of AML, renal cell carcinoma (RCC), oncocytoma and metastasis of any other primary tumours are present. Fat-predominant and muscle-predominant AMLs may mimic liposarcoma and leiomyosarcoma, respectively, which are the most common types of retroperitoneal sarcomas. These lesions can be usually distinguished by their own radiological findings. For example, in T2 weighted MRI, smooth muscles are observed as hypointense signal in AML while hyperintense in RCC (18).

TSC is a multisystemic hamartomatous disease with autosomal dominant inheritance, affecting both adults and children. It is usually caused by a decreased or absent expression of TSC1 (hamartin) or TSC2 (tuberin) genes. The lack of hamartin-tuberin complex results in the development of tumours in a number of organs, including AML in the kidneys. Affected individuals have a high risk of developing various skin lesions, including facial angiofibromas, hypopigmented macules, shagreen patches and ungual fibromas. Bilateral and multifocal renal AMLs, consisting of abnormal vessels, immature smooth muscle cells, and fat cells, are one of the benign tumours of the kidney and develop in approximately 55%-75% of patients with TSC aged <10 years. In addition, RCCs may develop in various histological types in some patients with TSC. Although lifelong risk is similar to that in the general population (2%-3%), the age of onset of renal tumour is younger in patients with TSC (mean age, 36 years) (9). Although the majority of AMLs occur sporadically, this tumour occurs in 80%-90% of patients with TSC. TSC is caused by germline mutations of TSC1 on 9q34 and TSC2 on 16p13. Kidney AMLs related with TSC are frequently multifocal and bilateral. Mutations of TSC2 can also be seen in sporadic AML. AML is also associated with lymphangioleiomyomatosis (9). Although only 10%-20% of AML cases are associated with TSC, all patients should be investigated in terms of non-diagnosed or subclinical TSC. When compared with renal AML associated with TSC, sporadic renal AML usually occurs at an older age, usually single involvement, causes rare spontaneous haemorrhage and symptoms, and shows a slower growth course (19). TSC was not observed in any of our cases.

Because most of the AMLs are small and benign, the first option recommended in the current approach and in the European Association of Urology guidelines is active surveillance (9). However, the first choice in the indications of treatment is selective artery embolisation, and the surgical option should be only the final option. In any case, nephron protective surgery should be preferred (7).

In our study, all patients were followed up for a while, and the surgical method was then selected. Only two patients had partial nephrectomy. In the remaining five cases, radical nephrectomy was performed. According to their histological appearance, AMLs are classified as classic and epithelioid types. The classical type is observed more frequently (20). The major characteristic feature of CAMLs are abnormal thick vessel walls, which prevent the proper development of internal elastic lamina, smooth muscle-like cells and adipose tissue. These three components can be observed in different ratios, and some components may not be seen at all CAMLs. CAML is found primarily in the kidney, as well as in the spleen, liver, uterus and fallopian tubes (21). EAML is a monotypic type of AML that can mimic RCC and is clinically benign or malignant (aggressive and metastatic). It is distinguished from CAML by the presence of epithelioid component with abundant eosinophilic and granular cytoplasm. EAML may show malignant transformation, and it can manifest itself as local recurrence or distant metastasis. There is also a need for adjuvant therapy after surgery (22). However, there is no consensus on the epithelioid component ratio of the tumour for the diagnosis of EAML (10,20).

Aydin et al. (20) reported clinical and histopathological features of AML in 194 patients. EAML was found in 15% of the patients, nuclear atypia in 7%, and abnormal histological findings were also observed in 3.6%. The mean epithelioid component ratio was 51% in these patients. The presence of epithelioid component was higher in patients with TSC (27%) than in those with sporadic AML (7%). Local recurrence or distant metastasis was not observed in the study, which gave a mean follow-up of 5.1 years.

Four microscopic features are recommended in the EAML definition, which are as follows: presence of atypical epithelioid cells at ≥70%, ≥2 mitosis in the area of 10× magnification, atypical mitosis and necrosis. The presence of three or all of these features has a high predictive value for malignancy. With this model, 78% of the patients with malignant EAML and 100% of benign lesions can be distinguished (23).

There is no consensus as to the percentage of epithelioid cells required for diagnosing EAML, with some authors suggesting that only ≥5% of the cells must exhibit epithelioid histology, while others demanding at least 20% or even 80% (2,23,24). EAML was first described by Mai et al. (25) in 1996. In 2004, the WHO stated that EAML is a mesenchymal tumour with a potential for malignancy. Renal EAML is examined in two groups as pure sporadic EAML and TSC-associated EAML. EAML was found to have higher rate of association with TSC than with CAML (26).

Typically, AMLs are unencapsulated and well-circumscribed masses. The colour of the cut surface varies depending on the existing fatty content in the lesion. Fat-poor tumours appear

to be tan white to pink, while fat-rich ones are predominantly yellow. As the name implies, AMLs consist of three components: thick-walled vessels, smooth muscles and fat tissues. For the diagnosis of fat-poor lesions, the fat ratio of the tumour should be less than 25%. In some cases, hyalinisation, cystic change or calcifications have also been reported. Epithelioid cells may be found in very few cases. The presence of more than 70% atypical epithelioid cells, ≥2 mitoses per 10 high power fields, atypical mitotic figures and necrosis are associated with increased risk of malign behaviour (9).

Study Limitations

In our study, all cases were of CAML type. AML tumours were well separated from the normal kidney parenchyma. Thus, the structure was suitable for classical triphasic histology: it contained mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells. Mitotic activity, tumour necrosis, haemorrhage, extrarenal metastasis, lymphovascular and perineural invasion were not seen.

In addition to the epithelioid histology in EAML, epithelioid cells must have enlarged vesicular nuclei with prominent nucleoli. When the epithelioid component predominates and nuclear atypia is extensive, these tumours may be erroneously diagnosed as RCC or sarcoma. For this reason, it may be necessary to perform immunohistochemical studies to confirm the diagnosis of EAML (7). Moreover, in suspected cases, the renal tissue taken for biopsy can be analysed by specific immunohistochemical techniques. The smooth muscle component in AMLs is positively stained with mesenchymal markers such as vimentin and actin (8).

The smooth muscle morphology seen in AML is similar to sarcomatous RCC or leiomyosarcoma, making it difficult to interpret the biopsy. The development of smooth muscle-specific dyes and HMB-45 increased the reliability of percutaneous biopsy. HMB-45 immunoreactivity is a feature of perivascular epithelioid cell tumours; in fact, all AMLs are stained positive with HMB-45. RCCs are not stained with HMB-45. However, a small proportion of AMLs, especially epithelioid types, cannot be stained with HMB-45 (8). The cells often express smooth muscle markers as well, particularly SMA and, less commonly, desmin. However, the fat-poor tumours are typically negative for Melan-A. Staining for S-100 protein is usually negative. The majority of EAML cases demonstrate membranous and cytoplasmic staining of E-cadherin, whereas CAML cases demonstrate cytoplasmic staining alone. Moreover, in diagnostically challenging cases, staining for CD68 (PG-M1) and anti-melanoma antibody (PNL2) may be helpful in distinguishing renal EAML from other renal tumours. Some AML samples can be stained positive for CD-177 (27,28,29,30).

In our study, all cases (100%) were positive with HMB-45, Melan-A and SMA. No case was positive for S100 and cytokeratin staining.

Conclusion

Renal AMLs are mesenchymal kidney tumours and have triphasic histology. The most common group of patients with renal AMLs are middle-aged women. Generally, AMLs are asymptomatic and rarely become symptomatic. AMLs are unencapsulated and well-circumscribed masses. The colour of the cut surface varies depending on the existing fatty content in the lesion. As the name implies, AMLs consist of three components: thick-walled vessels, smooth muscles and fat tissues. HMB-45 immunoreactivity is a feature of perivascular epithelioid cell tumours; in fact, all AMLs are stained positive with HMB-45. The cells often express smooth muscle markers as well, particularly SMA and, less commonly, desmin.

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Ethics

Ethics Committee Approval: The study was approved by the University for the non-interventional Clinical Research Ethics Board (approval number: 05, date: 07.03.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: S.H., S.G., Critical Review: S.H., S.G., Concept: D.G., İ.E.S., Design: D.G., Data Collection or Processing: D.G., İ.E.S., Analysis or Interpretation: D.G., İ.E.S., S.H., Literature Search: D.G., İ.E.S., S.G., Writing: D.G.

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