Original Article

Adult renal angiomyolipomas: A retrospective analysis of the histological subtypes and their clinicoradiological correlates

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Abstract

Background: Renal angiomyolipomas (AMLs) are rare, benign mesenchymal tumors of the kidney. Asian data on the prevalence of the subtypes of AMLs and their association with tuberous sclerosis are sparse prompting us to evaluate the clinicopathological characteristics of these tumors.

Materials and Methods: We included cases diagnosed from 2001 to 2021 extracting demographic details, clinical presentation, syndromic association with tuberous sclerosis, and preoperative clinicoradiological features from the electronic medical records.

Results: Ninety-five cases of adult renal AML were diagnosed among 2402 renal tumors, a prevalence of 3.95%. Forty tumors (42%) were detected incidentally; two patients had life-threatening retroperitoneal hemorrhage. Tuberous sclerosis complex (TSC) was associated with ten cases (10.5%). These patients were a decade younger than those in the non-TSC group ($P = 0.008$) and had bilateral, multiple, and larger tumors ($P = 0.0009$, 0.001, and 0.047, respectively). Microscopically, classic and epithelioid subtypes were seen in 87 (91.6%) and 8 cases (8.4%), respectively. Hemorrhage was more common in the epithelioid subtype ($P = 0.13$). HMB-45, melan-A, and smooth muscle actin immunohistochemistry were useful in cases which lacked the prototypical classic histology and for confirming a diagnosis of epithelioid AML.

Conclusions: The prevalence of renal AML in our series was four times higher, and the mean age at diagnosis was a decade earlier than that reported in Western literature but similar to data from two Asian countries. Similar studies from other countries will help ascertain if these differences in prevalence can be attributed to ethnic differences.

Keywords: Angiomyolipomas, HMB-45, perivascular epithelioid cell tumors, renal, tuberous sclerosis

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INTRODUCTION

Renal angiomyolipoma (AML), a rare, benign mesenchymal tumor, belongs to the group of tumors known as perivascular epithelioid cell tumors (PEComas).[1] The clinical presentation ranges from incidental detection to life-threatening situations such as intratumoral hemorrhage leading to shock and hypotension (Wunderlich syndrome).[2] On occasion, AMLs pose significant diagnostic challenges when they mimic renal cell carcinoma (RCC).[3,4] An accurate preoperative diagnosis through recognition of

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clinicoradiological characteristics might be helpful in the identification of aggressive subtypes in order to provide optimal treatment; however, often, the diagnosis is finally made on histopathology.[4] Although there is a significant body of Western literature on renal AMLs, Asian reports are scarce, particularly with regard to the relative proportion of each histological subtype and their associations with tuberous sclerosis.[5] This prompted us to evaluate the clinicopathological characteristics of renal AMLs that were diagnosed in this institution over the past 20 years.

MATERIALS AND METHODS

This retrospective study from January 2001 to May 2021 was carried out in the department of general pathology and included 95 cases of adult renal AMLs diagnosed at a 2500-bedded tertiary care center in South India. Demographic details, clinical presentation, syndromic association with tuberous sclerosis, associated comorbidities, preoperative clinicoradiological diagnosis, associated renal or other malignancies, and type of surgical procedure performed were obtained from the electronic medical records of our institution. The diagnosis was based on histological features and additional immunohistochemical studies including HMB-45, smooth muscle actin (SMA), and melan-A in select cases. The tumors were divided into sporadic and those associated with tuberous sclerosis based on the 2013 diagnostic criteria.[6] Histopathological classification into classical and epithelioid subtypes of AML was based on the World Health Organization (WHO) 2016 Classification of Tumors of the Urinary System and Male Genital Organs.[7] The clinical features were correlated with these histological features. All procedures performed in the current study were approved by the Institutional Review Board (IRB) and Ethics Committee (Ref: IRB Min. No. 11762 dated January 7, 2019) in accordance with the 1964 Helsinki Declaration and its later amendments. Formal written consent was not required with a waiver from our IRB as this was a retrospective study of data with no identifying details of patients being revealed.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS (Statistical Package for the Social Services, IBM, New York, NY, USA) version 16.0. Categorical variables were reported using frequency and percentage, whereas mean ± standard deviation (SD) or median with interquartile range as appropriate was used for continuous variables; the association between the categorical variables was done using Chi-square statistics/Fisher's exact test where $P < 0.05$ was considered statistically significant. The comparison of renal AML–tuberous sclerosis association with the clinical presentations was analyzed using Chi-square if categorical and independent *t*-test/Mann–Whitney U-tests if continuous.

RESULTS

There were 95 cases of renal AML diagnosed among 2402 surgically resected renal tumors from 2001 to 2021, constituting a prevalence of 3.95%. The majority were females 67 (70.5%) with a male: female ratio of 1:2.4. The ages ranged from 14 to 68 years, with a mean age at diagnosis of 42.2 years (SD 11.5).

Clinical presentation and imaging

Fifty-five patients (58%) were symptomatic, whereas forty patients (42%) were asymptomatic, and their tumors were detected incidentally. The presenting symptoms included flank pain, palpable mass, hematuria, anemia, urinary tract infection, retroperitoneal hemorrhage, and renal failure. Two patients had life-threatening retroperitoneal hemorrhage leading to Wunderlich's syndrome. Four patients (4.2%) had diabetes, 13 (13.7%) had hypertension, and 7 (7.4%) had both hypertension and diabetes. Tumors ranged from 1–26 cm (mean: 8.1 cm (SD: 5.6). The mean tumor size of the incidental and symptomatic AMLs was 6.9 cm (SD: 4.5) and 8.86 cm (SD: 6.1), respectively ($P = 0.08$). Four cases had concurrent malignancies, namely diffuse large B-cell lymphoma (DLBCL), multiple myeloma, papillary thyroid carcinoma, and breast carcinoma, respectively. In 55 cases (57.8%), the preoperative diagnosis was AML, the majority of which were "fat rich" on histology. Of the 40 cases with a preoperative diagnosis of RCC, 19 were AMLs that were fat poor.

Tuberous sclerosis complex

Ten cases (10.4%) of renal AML had an association with tuberous sclerosis complex (TSC) and the remaining 85 cases (89.5%) were sporadic [Table 1]. Patients with TSC were younger, with a mean age of 36 years versus 42.9 years in the non-TSC group ($P = 0.008$). They more often had bilateral, multiple tumors and had significantly larger tumors, with a mean tumor size of 11.45 cm as compared to 7.67 cm in the non-TSC group ($P = 0.0009$, 0.001, and 0.047, respectively).

Surgery and gross findings

Among the 95 cases included in the study, 45 (47%) underwent partial nephrectomies. Twenty-nine (30.5%) had total nephrectomies and 21 (22%) had radical nephrectomies with a preoperative diagnosis of RCC. Two cases had an associated RCC – one in the ipsilateral kidney and the other in the contralateral kidney. Only one

had a focal breach of the renal capsule. Macroscopically, hemorrhage and cystic change were noted in 55 (57.8%) and 19 cases (20%), respectively, whereas 3 cases showed both areas of hemorrhage and cystic changes, and 18 cases showed neither. None of the cases were hilar vessels or ureter involved.

Microscopic findings and immunohistochemistry

Microscopically, 87 cases (91.6%) had features of classic subtype and 8 (8.4%) were of the epithelioid subtype. The classic AML showed all three elements, the thick-walled blood vessels, mature fat, and a perivascular arrangement of smooth muscle-like spindle cells [Figure 1]. The epithelioid AML (EAML) had cohesive nests or sheets of large polygonal to plump spindle-shaped cells with eosinophilic cytoplasm and round-to-oval nuclei. Multinucleated giant cells and prominent nucleoli were seen in 3/8 EAMLs [Figure 2]. There was an association of the presence of hemorrhagic areas with EAMLs, however, this was not significant ($P = 0.13$). Necrosis was seen in 2/8 cases. Nuclear atypia and mitotic activity were not seen in any of the eight cases of EAML [Tables 2 and 3]. None of the cases demonstrated microscopic tumor invasion of hilar vessels or the ureter. In 42 (44%) cases that lacked the classic triphasic histology and had a paucity of the adipocytic element, immunohistochemistry (IHC) was done for HMB-45, and in 30 of these cases, IHC for SMA was also done. HMB-45 was positive in 41/42 (97.6%) cases, with 29/30 of these also being immunopositive for SMA [Figure 3]. One case which was extensively hyalinized but had both obvious vascular and adipocytic elements was negative for both HMB-45 and SMA. The 42 cases included 8 EAMLs which were positive for both HMB-45 and melan-A [Figure 4]. Of the eight cases of EAML, six also had IHC for SMA and were found to be positive.

Table 1: A comparison of sporadic angiomyolipomas and those associated with tuberous sclerosis complex

	Associated with TSC (*n*=10)	Not associated with TSC (*n*=85)	*P*
Mean age at diagnosis (years)	36.2 (± 13.79)	42.9±11.05	0.008
Sex			
Male	2	26	0.71
Female	8	59	
Clinical presentation			
Incidental	4	36	1.0
Symptomatic	6	49	
Laterality			
Unilateral	5	80	0.0009
Bilateral	5	5	
Multiplicity			
Single	4	75	0.001
Multiple	6	10	
Mean tumor size	11.45±4.3	7.67±5.6	0.047

TSC: Tuberous sclerosis complex

Table 2: A comparison of the incidence of necrosis and hemorrhage in epithelioid and classic angiomyolipomas

	Epithelioid AML (*n*=8)	Classic AML (*n*=85)	*P* Fisher's exact test
Areas of necrosis			
Present	2	3	0.05
Absent	6	82	
Areas of hemorrhage			
Present	7	47	0.13
Absent	1	38	

AML: Angiomyolipomas

DISCUSSION

Renal AMLs are benign mesenchymal tumors of the kidney belonging to the family of lesions called PEComas.[1,8,9] Although benign, acute life-threatening presentation with spontaneous hemorrhage leading to shock and hypotension, as seen in two of our patients, has been reported before.[10,11] The sporadic form of AML, seen in 89.5% of cases, is typically detected incidentally on routine imaging for other illnesses or at autopsy and occurs as small, fat-rich, well-circumscribed tumors. AMLs associated with tuberous sclerosis, occurring in 10.5% of our cases, are frequently multiple and are associated with inactivating mutations in TSC1 and TSC2, leading to hyperactivation of the mammalian target of rapamycin signaling pathway.[12] The larger tumors are known to cause hemorrhage, particularly those associated with tuberous sclerosis, from rupture of pseudoaneurysms. They then present with hematuria, retroperitoneal hemorrhage, renal dysfunction, or even death from blood loss.[13] The mean age at diagnosis for sporadic AML is at least a decade later than those associated with TSC.[14] This is similar to our series where AML patients with TSC presented a decade earlier than those with sporadic AML.[7,15]

Demography of angiomyolipoma

The prevalence of AML as reported by the WHO is about 1%, and this is in contrast to our prevalence of 3.95%. Our true prevalence is likely to be even higher as only surgically excised tumors were studied and smaller tumors with typical findings on radiology were followed up in the outpatient clinic. The higher prevalence in our series could be because our center is a tertiary care referral hospital and there could be a selection bias.[7] While a very strong female preponderance with a female-to-male ratio of 4:1 has been reported,[7,16] we found a more modest female predominance with a female-to-male ratio of 2.4:1; this could be because of differences in ethnicity. We also found that a lower mean age at diagnosis of the entire cohort was 42.2 years compared to 54 years reported by a few

Table 3: Pathological features of the eight epithelioid angiomyolipomas

Age/gender	Size (cm)	Tuberous sclerosis	Cysts	Hemorrhage	Necrosis	Cellular atypia	Ureter/hilar vessels involved
39/male	4.0	No	Yes	Yes	No	No	No
54/male	3.0	No	No	No	No	No	No
37/female	4.0	No	Yes	Yes	No	No	No
56/female	20	No	Yes	Yes	Yes	No	No
45/male	11.8	No	No	Yes	Yes	No	No
34/male	6.0	No	No	Yes	No	No	No
31/female	4.0	No	Yes	Yes	No	No	No
64/male	4.0	No	No	Yes	No	No	No

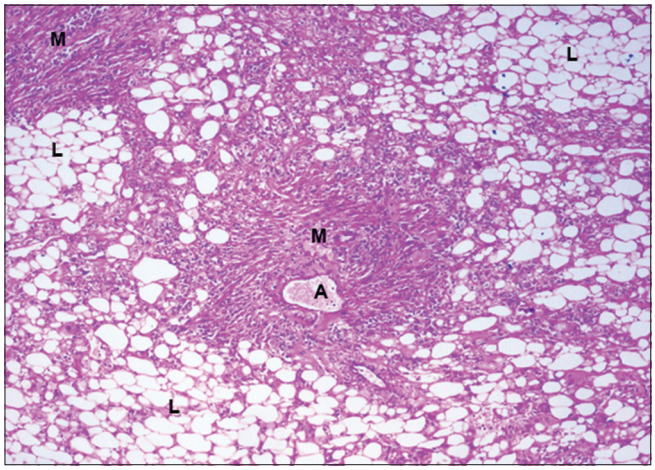

Figure 1: Photomicrograph of an angiomyolipoma with the classic triphasic histology, illustrating all the three components, the vasculature (A), the smooth muscle (M), and the adipose tissue (L) (hematoxylin and eosin ×40)

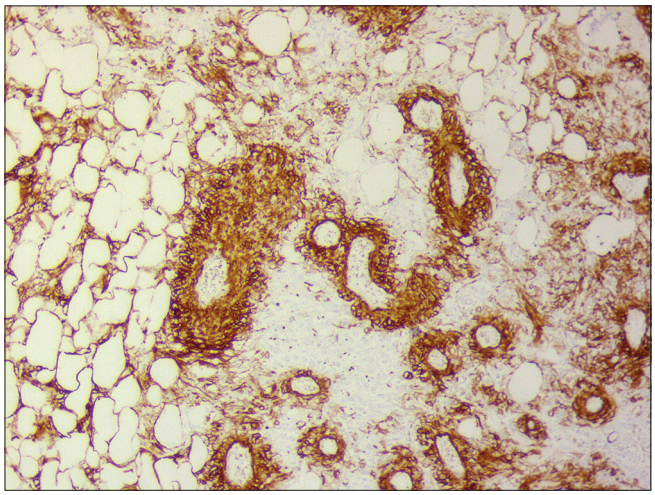

Figure 3: Photomicrograph illustrating the immunopositivity of tumor cells for smooth muscle actin in a renal angiomyolipoma highlighting the perivascular arrangement that is a characteristic feature of angiomyolipomas (avidin peroxidase ×100)

other studies,[16] however, ours was similar to that reported by a study from India and another from Korea.[17,18] In the present study, AML cases associated with tuberous sclerosis (36.2 ± 13.8 years) were a decade younger at diagnosis than sporadic cases (43 years ± 11), which was in concordance with the WHO data.[7,15]

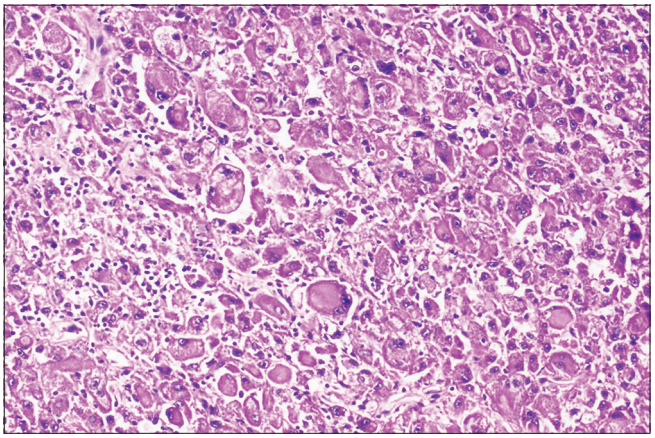

Figure 2: Photomicrograph of an epithelioid angiomyolipoma highlighting the large polygonal tumor cells and scattered multinucleated giant cells (hematoxylin and eosin ×100)

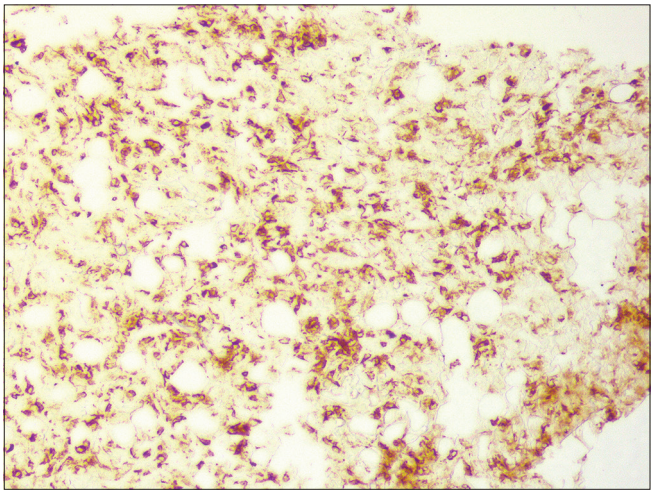

Figure 4: Photomicrograph illustrating the diffuse strong cytoplasmic immunopositivity of tumor cells for HMB-45 in an epithelioid renal angiomyolipoma (avidin peroxidase ×100)

Clinical presentation and comorbidities

In this study, 42% (40 cases) of AMLs were incidentally detected and 58% (55 cases) were symptomatic. Flank pain and hemorrhage were among the common presenting symptoms, which was in concordance with Indian,[17] Middle Eastern,[19] and Western data.[20-22] The association of hypertension with AML,[23] probably due to external compression of the renal artery by the tumor[24] or from

ischemic effects caused by renal parenchymal compression or related diabetic nephropathy,[25] was also noted by us with 25% of cases having either diabetes or hypertension.

Preoperative diagnosis and surveillance

In the presence of abundant fat, renal AMLs may be recognized on ultrasound and computed tomography, however, when there is paucity of fat, diagnostic differentiation from RCC can be difficult.[4,26] In our study, the preoperative diagnosis was incorrect in 40 cases, 19 of which were fat poor. The diagnostic accuracy was better when the AMLs were rich in fat. There is limited literature on the usefulness of computed tomography and magnetic resonance imaging in differentiating AML from other renal tumors, but recent studies show promising results for detecting lipid-poor AMLs and may play a role when contemplating active surveillance versus biopsy.[27-29] A large retrospective study on small AMLs[30] suggested that concerning features on ultrasound include irregular tumor borders, presence of calcification, extension beyond the renal capsule, and a size >4 cm. The slow annual growth rate of about 0.27 mm prompted these authors to suggest that subcentimeter asymptomatic AMLs, with no concerning ultrasound features, do not need further characterization or follow-up. While further imaging/biopsy is recommended for lesions >1 cm, routine surveillance is not indicated for those <3 cm if characterized as AMLs. The slow growth rate of AMLs was also reported by Courtney *et al*.[31] and Swärd *et al*.[22] who found that the natural growth pattern of sporadic renal AMLs in patients without tuberous sclerosis averaged 0.015 cm per year and 2.7 mm/year, respectively. Clinicians need to be aware that there is a 20% risk of hemorrhage in patients managed with active surveillance with a higher risk in tumors ≥5cm.[22]

Associated renal or other malignancies

In keeping with Knudson's two-hit hypothesis, renal AMLs may occur with increased frequency in the MEN1 population.[32] Concurrent malignant renal neoplasms with AMLs have been known to be associated with tuberous sclerosis.[33] Of 95 cases in the present study, 2 cases were associated with RCC, one on the same side and one on the contralateral side. The case with ipsilateral RCC was associated with tuberous sclerosis, an association that has been reported by others as well.[33-35] An additional four of our cases had concurrent malignancies, namely papillary thyroid carcinoma, diffuse large B cell lymphoma (DLBCL), carcinoma breast, and multiple myeloma.

In the present study, of the 85 unilateral tumors, right-sided tumors (48, 50.6%) appeared to occur more frequently than left-sided tumors (37, 38.9%). Ten (10.5%) cases had bilateral tumors. Compared to sporadic cases, bilateral tumors were more often associated with tuberous sclerosis (P = 0.0009), a finding well brought out by a multicenter study on patients with tuberous sclerosis; 52% had renal AMLs, 88% of the which were multiple and 83% bilateral.[36]

Multiplicity and size of tumors

Multiple lesions were seen in 16 (16.8%) cases in the present study and were seen more often in those associated with tuberous sclerosis (P = 0.001). We had one patient with a sporadic, multicentric AML who had para-aortic lymph node deposits that may be considered to be an expression of the multicentric nature of this disease rather than a metastatic deposit as the patients' tumor did not exhibit aggressive behavior. This finding is corroborated by others stating that multifocal lesions are not associated with malignant behavior and do not confer an adverse prognosis.[16,37-39] We found that larger tumors were significantly associated with tuberous sclerosis (P = 0.047). Although there is a suggestion that tumors >4cm in size are more likely to be symptomatic,[16,20] this was not our finding. Dickinson *et al*.[40] found that tumors greater than 8 cm were associated with significant morbidity, and on the other hand, AMLs that were 4–8 cm were variable in their behavior. All tumors in this study were well-circumscribed tumors except one that had a focal capsular breach in a patient with tuberous sclerosis.

Gross appearance

While prominent cystic changes may be seen in renal AML,[41] only 19 (20%) of our cases showed this finding, but hemorrhage was very common, seen in 57.8% of cases.[11,17] None of our cases had gross involvement of hilar vessels and ureter, a feature that may be demonstrated by renal AMLs that show an aggressive behavior with extension into the renal vein or inferior vena cava.[42]

Histological features

Classical angiomyolipomas

In our study, AMLs had a classic histology in 91.6% of cases and only 8.4% displayed epithelioid features. This is in concordance with the study done by Aydin *et al*.[43] and the WHO data.[41] Microscopically, classic AML is characterized by thick-walled blood vessels, adipocytic cells, and a perivascular arrangement of smooth muscle-like spindle cells. The smooth muscle cells appear to radiate from the blood vessel walls.[41] When either the smooth muscle-like cells or the lipid-laden predicted environmental concentrations predominate, they are known as leiomyoma-like AMLs or lipoma-like AMLs, respectively, but need to be differentiated from smooth muscle or

lipomatous tumors.[44,45] On occasion, microhamartomatous, intraglomerular, lymphangiomyomatous, or sclerosing areas are also present and may be considered minor subtypes.[44,46,47]

Epithelioid angiomyolipomas

Rarely, particularly in AML with TSC, tumors may display a predominant epithelioid morphology[38] with conspicuous cytologic atypia and multinucleation. In our study, all the epithelioid subtypes showed epithelioid cells, which were polygonal with eosinophilic cytoplasm and vesicular nuclei and some with prominent nucleoli. Hemorrhagic areas were seen in 7/8 EAMLs, an association noted by others.[37] EAMLs are more frequently malignant, and most malignant AMLs show epithelioid morphology.[38,43] Mitotic activity and focal necrosis indicate overt malignancy with aggressive behavior and metastasis within the abdomen or to the lung demanding close follow-up. Brimo *et al*.[38] suggest that the presence of at least three of the following criteria helps in differentiating benign from malignant EAML: (i) ≥70% atypical epithelioid cells, (ii) ≥2 mitotic figures/10 high-power fields, (iii) atypical mitotic figures, and (iv) necrosis. Two of our cases of EAML showed necrosis, however, neither showed other histological features of atypia or of mitotic activity, indicative of aggressive behavior. Factors associated with a higher incidence of metastasis include association with TSC, tumors ≥ 7 cm, extension through the renal capsule or into the renal vein, carcinoma-like pattern, and necrosis.[8] The presence of 4–5 of these features confers a very high risk for metastasis.

Immunohistochemistry and differential diagnosis

Typical or classical AMLs usually do not pose difficulty in diagnosis, however, given the wide spectrum of histological subtypes, particularly the "lipoma-like" and leiomyoma-like AMLs, the differential diagnoses include liposarcoma and leiomyoma/leiomyosarcoma. In these instances, IHC for melanocytic markers HMB-45 and melan-A and cathepsin K are useful.[12,44] Among those cases in which IHC staining was performed, HMB-45 was positive in 97.6% of cases and was seen in all 8 cases of the epithelioid subtype. The one case that was negative for HMB-45 was extensively hyalinized but had both obvious vascular and adipocytic elements.

Differentiation of EAMLs from clear cell RCC and urothelial carcinoma can be difficult particularly in the presence of sarcomatoid dedifferentiation and a relative lack of the epithelial component. In such cases, immunostaining for cathepsin K, HMB-45, and melan-A is helpful.[44] And finally, differentiation from translocation RCC, particularly t(6–11) RCC that stains for PAX8 and weakly for pancytokeratin, is often required as EAMLs are negative for these two immunomarkers.[48]

CONCLUSIONS

In this study spanning two decades, AMLs were seen in 3.95% of surgically resected renal tumors in this series, had a female preponderance, and were associated with tuberous sclerosis in 10.5% of cases. Patients with TSC were younger and more often had bilateral, multiple tumors that were larger than their sporadically occurring counterparts. The epithelioid subtype occurred in 8.4% of cases and was often associated with intratumoral hemorrhage. Immunohistochemical profile showed co-expression of smooth muscle actin and HMB45 and was useful in confirming the diagnosis in cases that lacked clear cut triphasic histology as well as in EAMLs. The prevalence of renal AML in our series was four times higher, and the mean age at diagnosis was a decade earlier than that reported in Western literature. Prevalence studies from other Asian and Middle Eastern countries will help ascertain if these differences in prevalence can be attributed to differences in ethnicity.

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Conflicts of interest

There are no conflicts of interest.

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