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Epithelioid angiomyolipoma of the kidney: pathological features and clinical outcome in a series of consecutively resected tumors

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The 2004 World Health Organization classification of tumors defines epithelioid angiomyolipoma of kidney as a potentially malignant mesenchymal neoplasm with reported metastasis in approximately one-third of the cases. However, this conclusion was based primarily on individual case reports and small retrospective series. More recently reported larger series have shown varying results. We reviewed 437 consecutive renal angiomyolipomas with primary resection at three tertiary-care institutions with high nephrectomy volumes. Only tumors showing >80% epithelioid histology were included in this study. Tumors resected elsewhere and reviewed in consultation were not included. Twenty of these 437 (4.6%) were classified as epithelioid angiomyolipoma. The female to male ratio was 11:9, mean age 49.7 (range, 30–80) years, and mean tumor size 8.7 (range, 1–25) cm. Microscopic tumor necrosis was present in 10 (50%) tumors and mitotic activity (range, <1–5/10 high power fields) in 8 (40%); atypical mitoses were seen in only 1 (5%) tumor. Pleomorphic ganglion-like or multinucleated giant cells were seen in 18 (90%) tumors. With a mean follow-up of 82.5 (range, 1–356) months, seventeen patients were alive with no-evidence-of-disease at the time of last follow-up; two patients died of unrelated causes with no-evidence-of-disease, and one patient (5%) developed distant metastases. Our data, based on consecutively resected angiomyolipomas with long clinical follow-up, suggests that epithelioid angiomyolipomas constitute a small proportion of all angiomyolipomas, and the rate of aggressive behavior among epithelioid angiomyolipomas, even when showing morphologic features previously reported to portend aggressive clinical behavior, is very low.
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The usual or classic renal angiomyolipoma (AML) is a benign mesenchymal tumor composed of a variable proportion of fat, spindle and epithelioid smooth muscle cells, and abnormal thick-walled vessels.[1] A number of morphologic variants of AML have been described in literature that include epithelioid, oncocytic, fat-predominant, smooth muscle-predominant, AML with epithelial cysts and sclerosing types.[2–4] The 2004 World Health Organization (WHO) Classification of Renal Neoplasms defines epithelioid-AML as a potentially malignant mesenchymal neoplasm, characterized by a proliferation of predominantly epithelioid cells[5] with approximately one-third of patients experiencing metastases, in contrast to the classic AML that is considered benign. However, this reported malignant potential was primarily based on case reports or small series of cases.[6–10] Recently, three relatively large series of epithelioid-AML have been published with conflicting results (Table 1).[11–13] While none of the cases in the series by Aydin *et al*[11] showed malignant behavior, the series by Brimo *et al*[12] and Nese *et al*[13] reported disease progression in a significant proportion of cases. However, the criteria for case selection varied among these series. The series by Aydin *et al*[11] included cases with any epithelioid features

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Table 1 Summary of the large series of renal epithelioid-AML reported in the literature

Study	No. of tumors	Size: mean (cm) (range)	% Epithelioid cells: mean (range)	Nuclear atypia	Mitosis: incidence range atypical	Necrosis, % tumors	Follow-up: Available	Follow-up: Mean (months) (Range)	Adverse outcome
Aydin *et al*[11]	15	8.6 (1–30)	51 (10–100)	93%; Diffuse: 40%, Focal: 53%	47%; 0–10/10 HPF: 6.7%	27	15/15	61.2 (1–239)	0
Brimo *et al*[12]	40 (at least 26 consultation cases)	7.2 (1–17.7)	68 (5–100)	58.4%; severe: 65%	72.5%; 1–6/10 HPF: 17%	37.5	34/40	34 (1–156)	26% recur/mets, 4 DOD, 4 AWD
Nese *et al*[13]	41 (No. of consultation cases-not reported)	11.9 (2–37)	Pure	Pattern A: 50%, B: 37.5%; A/B: 12.5%	79%; 0–13/50 HPF	73	33/41	44.5 (4–240)	17% recur, 49% mets, 33% DOD

Abbreviations: AML, angiomyolipoma; AWD, alive with disease; DOD, dead of disease; mets, metastasis; recur, recurrence.

(range 10–100%), with only 3 of their 15 tumors containing 80% or more epithelioid component. The other two series[12,13] included many consultation cases, potentially with selection bias for particularly unusual cases, either due to their histologic features or their clinical behavior. Based on their study design, these series do neither establish the true incidence of epithelioid-AML, nor the true incidence of aggressive clinical behavior among all resected, well-defined epithelioid-AML.

Our study was designed to establish the true incidence of epithelioid-AML, and based on all consecutive cases of AML with resection at our institutions, to investigate the incidence of aggressive clinical behavior.

Materials and methods

After Institutional Review Board approval, all tumors classified pathologically as renal AML and resected at Memorial Sloan-Kettering Cancer Center (MSKCC), Mayo Clinic, Rochester, and Massachusetts General Hospital (MGH) over periods of 18 (1992–2010), 35 (1975–2010), and 20 (1990–2010) years, respectively, were retrieved from the surgical pathology archives. Available material on all the cases was reviewed by dedicated GU pathologists at each institution.

Morphologic criteria for designating tumors as epithelioid-AML were based on the 2004 WHO classification, which defines it as a proliferation of predominantly round to polygonal epithelioid cells with enlarged vesicular nuclei, often with prominent nucleoli. In our study, only tumors with $\geq 80\%$ of epithelioid cells were considered as epithelioid-AML. While Nese *et al*[13] have recently considered only the tumors with $>95\%$ epithelioid components as epithelioid-AML, we chose 80% cutoff so that tumors falling outside the former more rigorous definition that have been reported to behave aggressively[12] are not missed. We excluded triphasic tumors with focal clear cell epithelioid histology, AMLs with foci of bland epithelioid cells embedded in a background of sclerosis, sclerosing AMLs, and oncocytoma-like AMLs for the purpose of this study (total, 36 tumors) (Figure 1). In our opinion, inclusion of all these variants would result in classification of a large number of cases with reported benign clinical behavior as epithelioid variant, defeating the main purpose of this study. Cases of peri-renal AML without renal involvement, as well as tumors resected elsewhere who came to our institutions for second opinion or for further management, were also excluded.

Clinicopathologic features recorded included age, gender, tumor size, peri-renal and/or sinus fat invasion, renal vein involvement, margin status, adrenal and lymph node involvement, presence of other concurrent renal tumors, presence or absence of gross or microscopic necrosis, mitotic count ($\times 10$ high power fields in the mitotically most active areas), atypical mitoses, nuclear atypia (defined as atypical polygonal cells with abundant cytoplasm, vesicular nuclei, prominent nucleoli, and nuclear size exceeding $\times 2$ size of the adjacent nuclei)[12] (Figure 2), and the presence of multinucleated cells and ganglion-like cells. Many of these features have been suggested to be harbingers of aggressive clinical behavior in epithelioid-AMLs.[12,13]

Majority of the tumors had immunohistochemical studies available including HMB45 (Ventana, clone HMB45), Melan-A (Ventana, clone A103), MiTF (Vector, clone 34CA5, 1:50), smooth muscle actin (SMA) (Vector, clone SMA, 1:50), desmin (DAKO, clone D-33, 1:50), and cytokeratins CAM5.2 (BD, clone CAM5.2, 1:50), AE1/AE3 (Ventana, clone AE1/AE3/PCK26), 34BE12 (Ventana, clone 34BE12), EMA (Ventana, clone EMA), and S-100 (DAKO, polyclonal, 1:500). Unless otherwise specified, the antibodies were pre-diluted. If immunohistochemical studies had not been performed previously, these were not performed as additional work-up for this study. Clinical follow-up data were gathered from medical records (MGH, Mayo Clinic) or from a prospectively maintained clinical renal database (MSKCC).

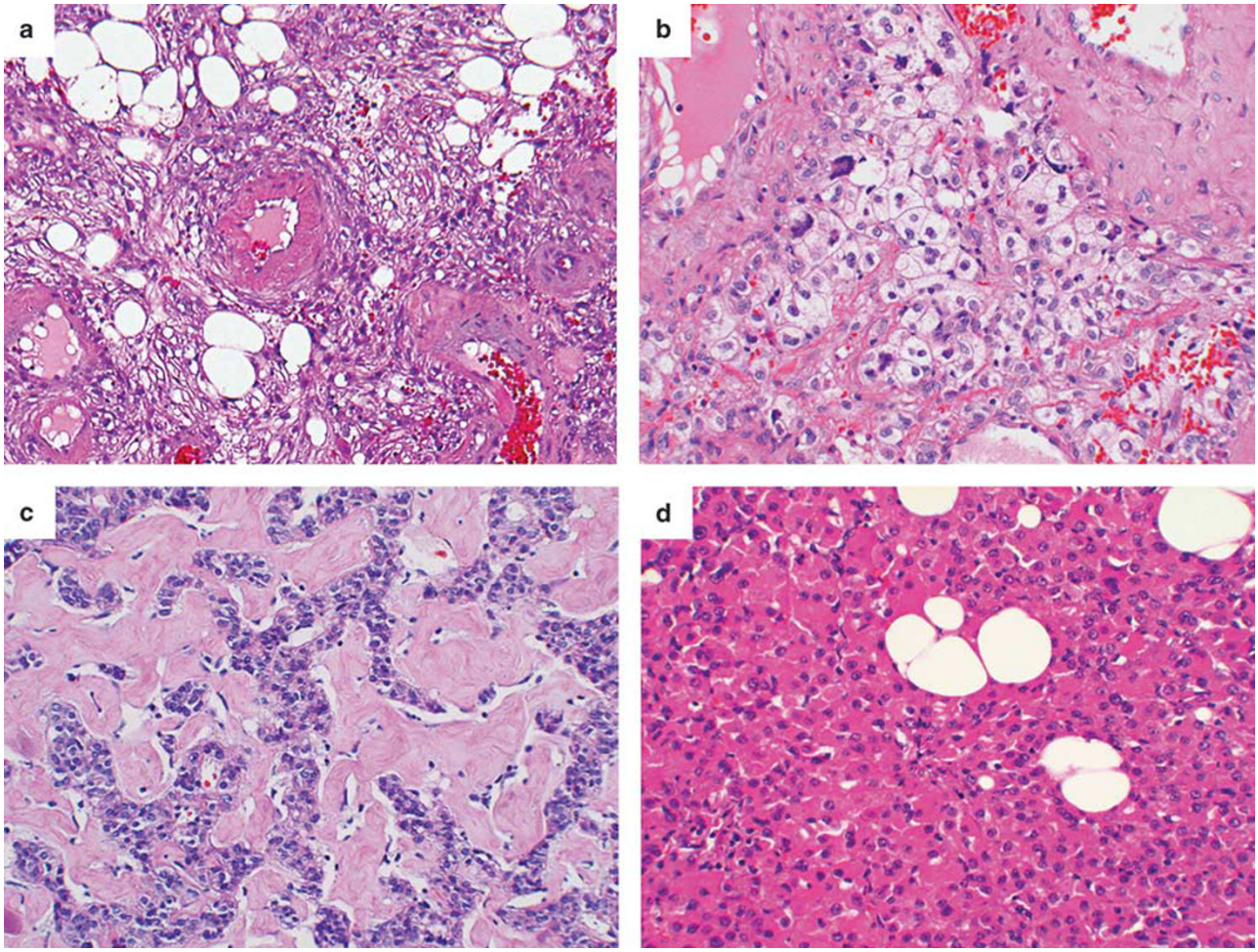

Figure 1 Tumors that were excluded from the study. (**a**) Classic angiomyolipoma (AML) with triphasic histology. (**b**) Classic AML with focal clear cell histology. (**c**) Sclerosing AML with bland epithelioid cells embedded in a background of sclerosis. (**d**) Oncocytoma-like AML. Note the banal appearance of the epithelioid cells in these examples.

Results

In total, 437 renal AMLs resected at our three institutions over periods of 18, 35 and 20 years, respectively, were reviewed; only twenty of these were classified as epithelioid-AML. Thus, the incidence of epithelioid-AML among all resected AMLs was 4.6%, ranging from 2.7–5.8% among the three institutions. The clinicopathological features are summarized in Table 2. The mean age at presentation was 49.7 (range, 30–80) years, with a F:M ratio of 11:9.

The tumor size ranged from 1–25 (mean 8.7) cm. The gross appearance of epithelioid-AML, as described in the pathology reports, was quite variable. However, the tumors were predominantly solid and most, though not all, contained areas of hemorrhage and possible necrosis (Figure 3).

On microscopic examination, epithelioid cells with enlarged vesicular nuclei and prominent nucleoli (nuclear atypia) were present in all, and constituted at least 80% of the tumor. Ganglion-like or multinucleated giant cells were identified in 89% of the tumors. Mitotic figures were present in 40% (1–5/10 HPF), while atypical mitoses were identified in only one tumor. Microscopic necrosis was seen in 50% of the tumors (Figure 4). Among the tumors in which these could be determined 2 of 9 showed renal vein invasion and 5 of 9 invaded peri-renal or renal sinus fat; one tumor showed both the renal vein and renal sinus fat invasion. Margins were free of tumor in all the cases. Adrenal gland (six cases) and regional lymph nodes (six cases) were uninvolved in the cases in which these had been removed.

Follow-up data was available on all 20 patients with epithelioid-AML. Over a mean follow-up of 82.5 (range 1–356) months, one patient (5%) developed distant metastases; 17 were alive with no-evidence-of-disease at the time of last follow-up and two patients died of unrelated causes. The only patient with tumor progression (case #6) was found to have multiple liver masses 13 months after the primary renal tumor was resected. The primary renal tumor in this case measured 19 cm, showed 100% epithelioid histology, and was composed

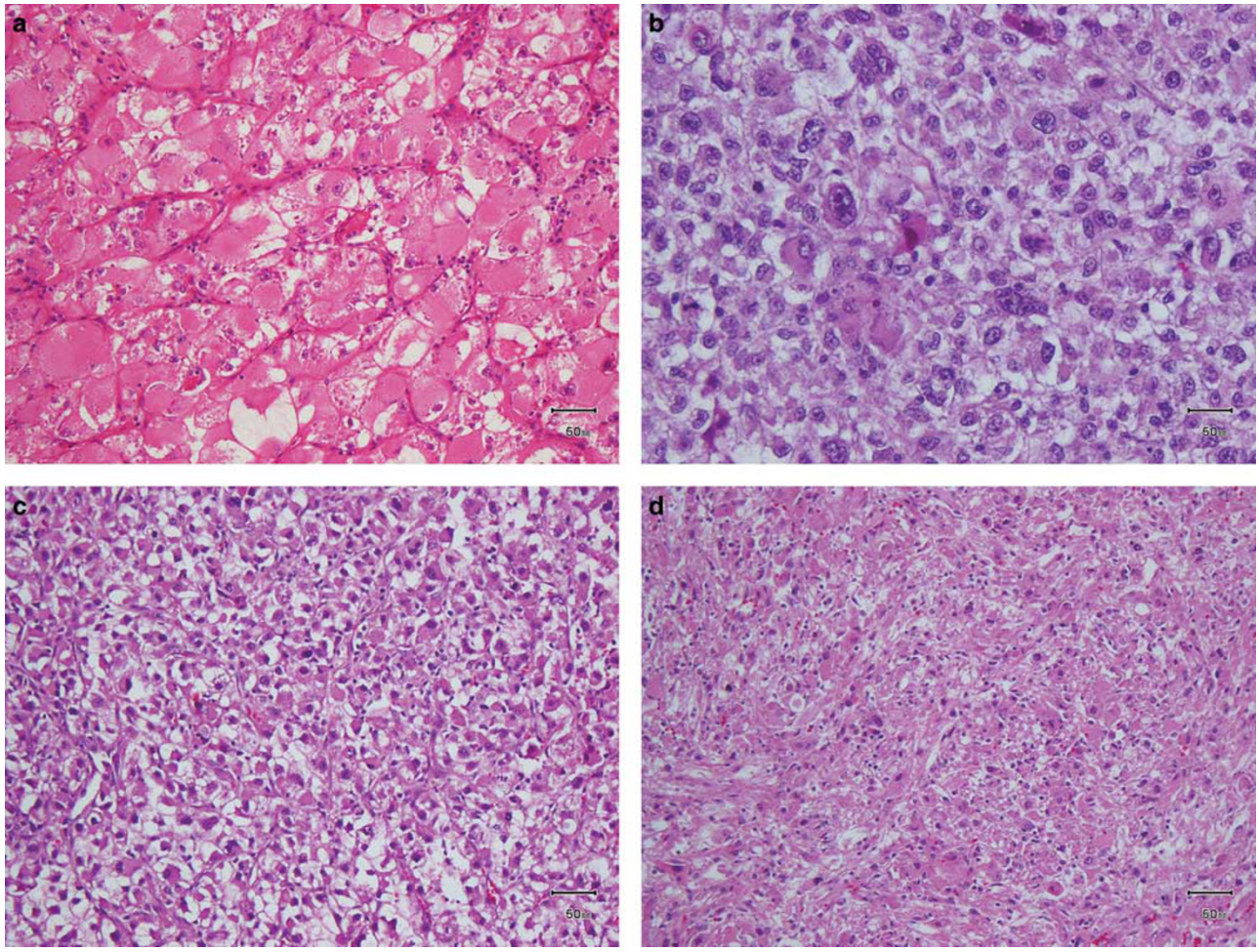

Figure 2 Spectrum of morphologic features of epithelioid cells in epithelioid angiomyolipoma. (**a**) Large cells with abundant pink cytoplasm and focal partial cytoplasmic clearing. (**b**) Cells with amphophilic to clear cytoplasm. (**c**) Cells with rhabdoid appearance. (**d**) Large epithelioid cells with abundant pink cytoplasm and focal spindling.

almost entirely of atypical cells with vesicular nuclei, and prominent nucleoli. It also contained multinucleated tumor giant cells, and showed extensive necrosis. However, no mitotic figures were observed in the tumor, and no renal vein, renal sinus vein, or peri-renal/sinus fat invasion were identified grossly or on microscopic evaluation. Fifteen lymph nodes removed in this case showed no evidence of AML. The tumor cells were immunoreactive for melanocytic markers (Figure 5). Fine needle aspiration of one of the metastatic liver masses revealed epithelioid tumor cells with similar cytological features and immunohistochemical profile as in the primary renal tumor (Figure 5). Among all the other reviewed cases (including 417 non-epithelioid (usual) angiomyolipomas), none had any adverse event at the last follow-up.

Discussion

Classic AML is a triphasic tumor characterized by a mixture of fat, spindled smooth muscle cells, and dysmorphic vessels. The classic examples are often found incidentally and are relatively easy to identify on imaging studies because of the presence of fat in them. Owing to their non-aggressive behavior, they are rarely resected until they reach a size where the possibility of rupture and hemorrhage is significant. Even in latter scenarios, many are embolized rather than resected. Thus, it is not surprising that many of the resected cases have a predominance of one of the components with paucity of others as they are likely to have atypical imaging features. In our experience, fat-predominant (mimicking lipoma or liposarcoma), and muscle-predominant (mimicking a smooth muscle neoplasm) comprise over 25% of resected AMLs. Since the first cases of epithelioid-AML were reported in1990s,[14,15] many others have been documented in the literature. However, most of these have been in the form of case reports or small series of <6 cases.[6–10] More recent larger series included epithelioid-AMLs seen predominantly in consultation by genitourinary pathologists or by clinicians at tertiary-care institutions. While they provide unequivocal evidence that epithelioid-AML

Table 2 Detailed clinicopathological characteristics and clinical outcomes of renal epithelioid angiomyolipoma cases

Case	*Age*	*Sex*	*Tumor size (cm)*	*Epithelioid cells (%)*	*Ganglion-like or multinucleated giant cells*	*Nuclear atypia*	*Mitosis/10 HPFs*	*Necrosis*
1	80	F	3	90	Present	Yes	1	No
2	51	F	1.9	90	Present	Yes	0	No
3	71	M	10	80	Present	Yes	0	No
4	41	F	5.5	99	Present	Yes	1	Extensive
5	56	M	19	100	Present	Yes	0	Extensive
6	43	M	19	100	Present	Yes	0	Extensive
7	57	F	8.2	100	Present	Yes	5[a]	Extensive
8	49	M	3	90	Present	Yes	1	No
9	45	M	10	100	Present	Yes	0	Extensive
10	63	F	5.5	95	Present	Yes	0	Focal
11	47	F	4.9	95	Absent	Yes	0	No
12	34	F	15	90	Present	Yes	0	No
13	76	M	7	90	Present	Yes	0	Extensive
14	33	M	7.5	100	Present	Yes	0	No
15	71	F	2.5	95	Present	Yes	0	No
16	31	F	9.2	95	Absent	Yes	1	Extensive
17	30	F	1	100	Present	Yes	0	No
18	39	F	4	80	Present	Yes	1	No
19	35	M	13	100	Present	Yes	1	Extensive
20	41	M	25	95	Present	Yes	1	Extensive
Total	Range, 30–80; mean, 49.7	M, 9; F, 11	Range, 1–25; mean, 8.7	Range, 80–100; mean, 94%	Present, 18/20 (90%); absent, 2/20 (10%)	Yes, 20/20 (100%)	Present, 8/20 (40%); range, 0–5	Present, 10/20 (50%)

Case	*Local invasion*	*Renal vein invasion*	*Margins*	*Adrenal*	*Lymph node*	*Concurrent renal tumor*	*Follow-up (month)*	*Outcome*
1	No	No	Free of tumor	N/A	N/A	1.1 cm AML	11.5	Alive, NED
2	No	No	Free of tumor	N/A	N/A	0.3 cm AML	27.5	Alive, NED
3	Peri-renal fat	No	Free of tumor	Unremarkable	0/9	No	3.5	Alive, NED
4	No	Yes	Free of tumor	Unremarkable	0/2	No	191	Alive, NED
5	Peri-renal fat	No	Free of tumor	N/A	0/22	No	33	Alive, NED
6	No	No	Free of tumor	N/A	0/15	No	15	Alive with liver metastasis
7	Sinus fat	Yes	Free of tumor	N/A	N/A	No	7.5	Alive, NED
8	Sinus fat	No	Free of tumor	N/A	N/A	No	63.5	Alive, NED
9	Sinus fat	No	Free of tumor	Unremarkable	0/1	No	1	Alive, NED
10	No	No	Free of tumor	N/A	N/A	No	50	Alive, NED
11	Sinus fat	No	Free of tumor	N/A	N/A	No	45	Alive, NED
12	No	No	Free of tumor	N/A	N/A	No	182	Dead, NED
13	Peri-renal fat	No	Free of tumor	Unremarkable	N/A	No	12	Dead, NED
14	No	No	Free of tumor	N/A	0/1	No	199	Alive, NED
15	No	No	Free of tumor	Unremarkable	N/A	1.2 cm AML	128	Alive, NED
16	No	No	Free of tumor	N/A	N/A	No	105	Alive, NED
17	No	No	Free of tumor	N/A	N/A	No	86	Alive, NED
18	No	No	Free of tumor	N/A	N/A	No	80	Alive, NED
19	No	No	Free of tumor	Unremarkable	N/A	No	54	Alive, NED
20	Peri-renal fat	No	Free of tumor	N/A	N/A	No	356	Alive, NED
Total	Peri-renal fat, 5 (25%); sinus fat, 4 (20%)	Yes, 2 (10%); No, 18 (90%)	Free, 20 (100%)	Not involved, 9/9 (100%)	Not involved, 6/6 (100%)	Present, 3/20	Range, 1–356; Mean, 82.5; Median, 52	Metastasis, 1/20 (5%); alive NED, 17/20 (85%); dead, NED, 2/20 (10%)

Abbreviations: AML, angiomyolipoma, classical; NA, not applicable/not removed; NED, no evidence of disease.
[a]Atypical mitoses present.

can behave in a malignant fashion, they provide very little information as to the proportion of AMLs that qualify as epithelioid-AML, or overall biologic behavior in all resected epithelioid-AMLs. In this study, we report the combined experience of three institutions that perform large volumes of nephrectomies; 20 epithelioid-AMLs represent only 4.6% of all (437) the consecutively resected AMLs at these institutions.

Three large series of epithelioid-AML have been published recently (Table 1).[11–13] The study by Aydin *et al*[11] included 15 tumors from a cohort of 194 consecutive AMLs resected at the Cleveland Clinic between 1981 and 2007. The incidence of epithelioid-AML among all AML cases was 7.7%. However, in this study the epithelioid component among cases designated as epithelioid-AML ranged from as low as 10% to 100% with an average of 51%. Only three tumors contained more than 80% epithelioid histology. In our experience, focal epithelioid morphology, as well as peri-vascular clear cell changes can be seen in a number of classic AMLs, and to date there is no data to suggest that this feature alters its usual benign biological behavior. There has been no consensus as to the percentage of epithelioid cells required for diagnosing epithelioid-AML although some investigators have suggested that at least 20% of

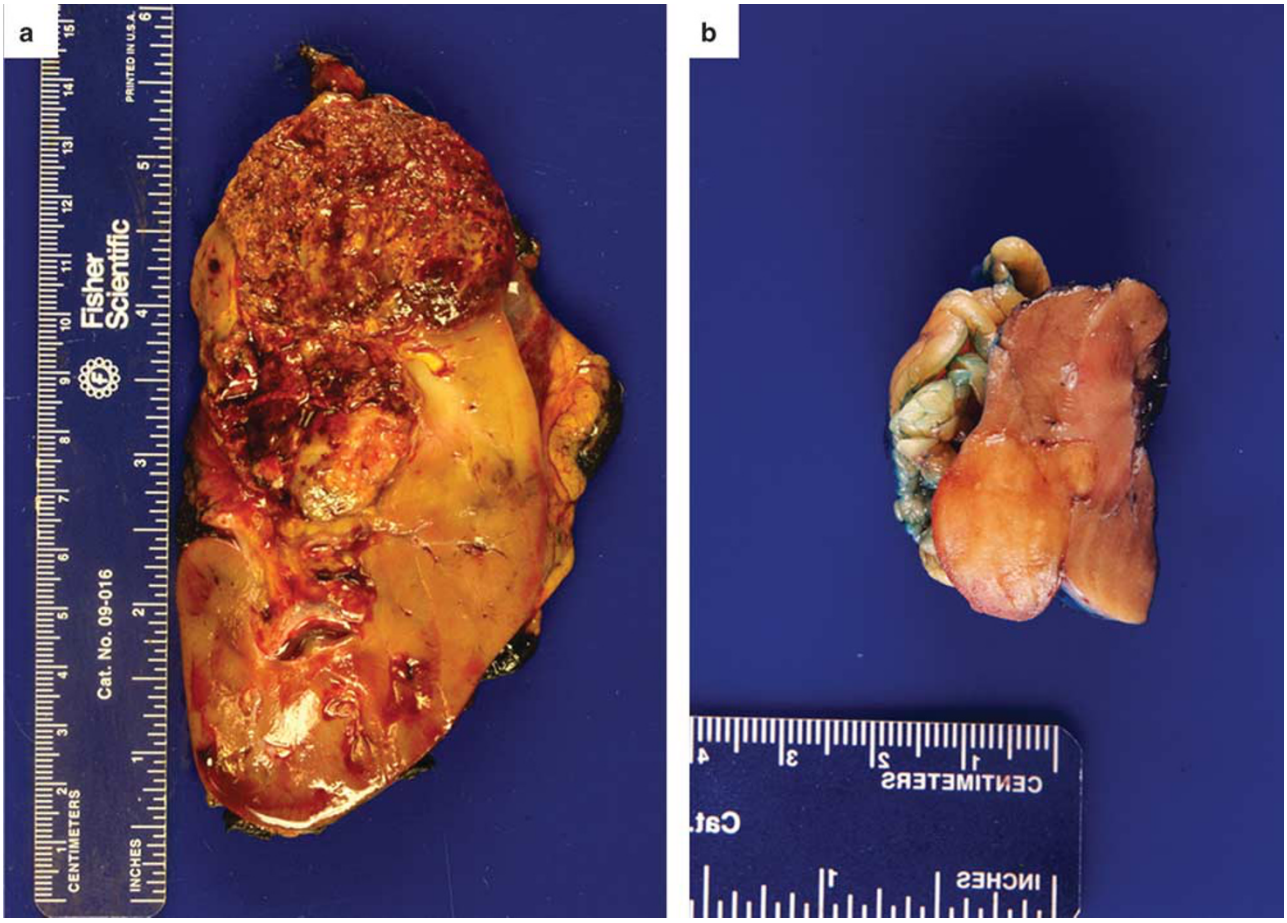

Figure 3 Range of the gross appearances in epithelioid angiomyolipoma (AML). (**a**) epithelioid-AML with gross. tumor necrosis and hemorrhage (Case 7). The tumor grossly invaded peri-renal and renal sinus fat. (**b**) A 1.9-cm solid mass with a homogenous cut surface (Case 2).

cells must exhibit epithelioid histology.[9,16] In addition to the epithelioid histology, such cells must have enlarged vesicular nuclei with prominent nucleoli. In the series reported by Aydin *et al*,[11] mean follow-up was 61 months and all patients had no evidence of disease at last follow-up. One could postulate that the universally benign behavior in this series might have been influenced by the relative low percentage of epithelioid histology in this group. At the same time, one reported case in literature that developed metastatic disease contained only 30% epithelial morphology;[6] however, this appears to be an extremely rare phenomenon. Based on the available literature, as well as the 2004 WHO definition of 'predominant', we included only those containing 80% or more epithelioid cells as epithelioid-AML. In a large series, Brimo *et al*[12] reported 40 cases of epithelioid-AML from Johns Hopkins, MD Anderson Cancer Center and the Cleveland Clinic. In this series, 26 of 33 tumors from Johns Hopkins were consultation cases. The percentage of epithelioid cells in these tumors ranged from 5–100% with a mean of 68%. Moderate to severe atypia was present in all tumors, as were mitoses and necrosis. Seven cases (18%) exhibited atypical mitotic figures. The follow-up data was available for 34 patients with a mean follow-up of 34 months. Twenty-six percent of the cases showed local recurrence or distant metastasis; four patients died of disease and four were alive with disease. The incidence of marked cytologic atypia, mitotic activity, and atypical mitotic figures was much higher in this study compared with that in our study on consecutively resected tumors. It is likely that the differences are attributable to the study population or design, in particular the consultation bias.

More recently, Nese *et al*[13] reported 41 epithelioid-AMLs from Cedars-Sinai Medical Center, Brigham and Women's hospital and multiple other centers within the US and abroad, including 16 previously published cases.[17] The number of consultation cases in this series has not been provided, but given the authors and institutions involved, it is an almost certain that a large number of these were consultation cases. The cases reported in this series were 'pure' with a minimal adipose component. Follow-up data

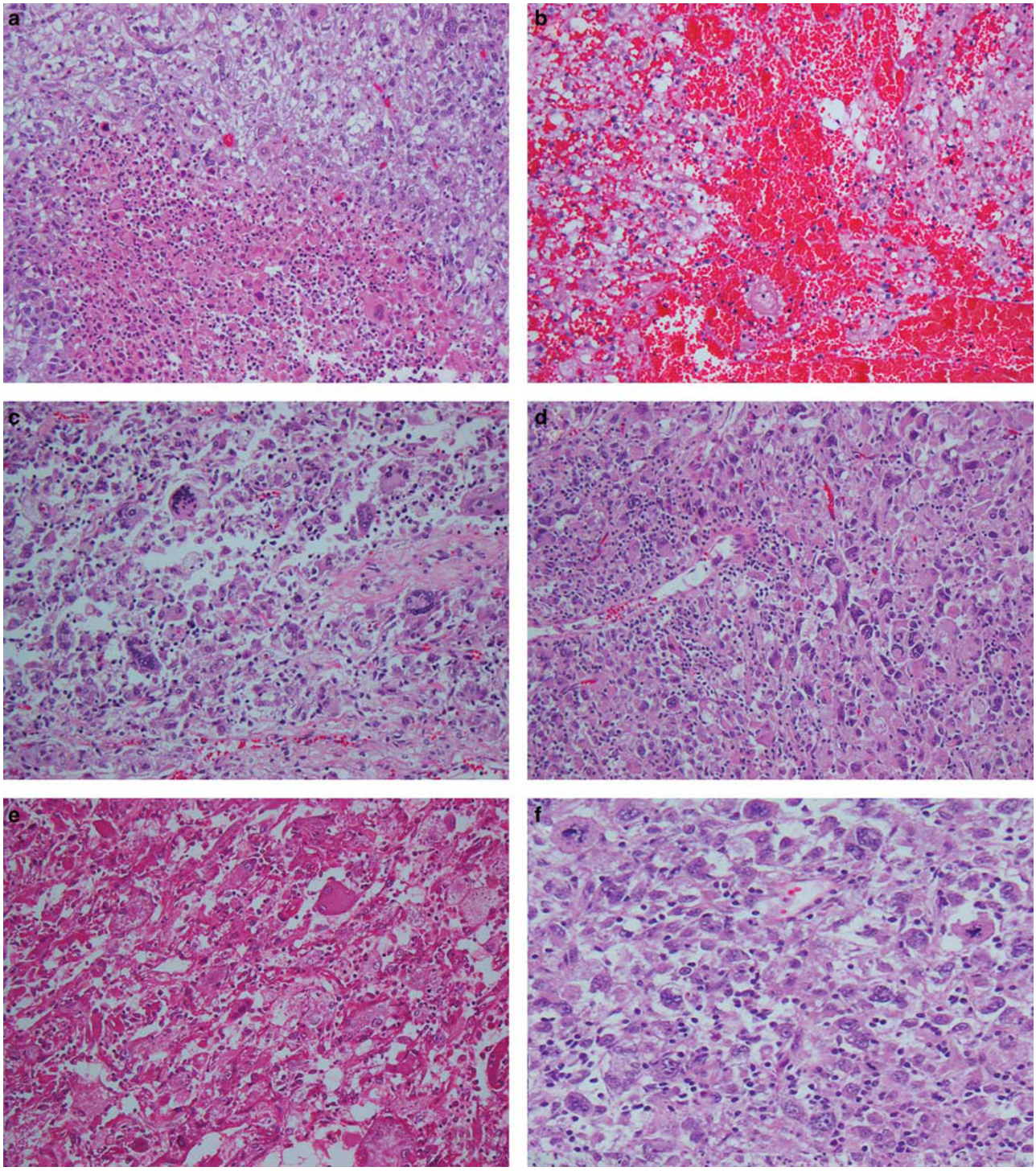

Figure 4 Histologic features of epithelioid-AML. (**a**) Coagulative tumor necrosis. (**b**) Intratumoral hemorrhage. (**c–e**) Giant cells; Histiocytic-like (**c**), Markedly pleomorphic (**d**), and with abundant granular, eosinophilic cytoplasm (**e**). (**f**) Mitoses and atypical mitotic figures.

available in 33 patients showed 17% and 49% experiencing local recurrence or metastasis, respectively. Thirty percent of the cases had metastasis at the time of the presentation and 33% died of disease. Based on these cases, the authors concluded that important prognostic factors include, (a) presence of tuberous sclerosis syndrome, (b) tumor necrosis, (c) extra-renal extension or renal vein invasion, (d) carcinoma-like histology, and (e) tumor size greater than 7.7 cm; 80% of their cases with three or more of these features showed aggressive behavior.[13] Brimo *et al*[12] suggest another predictive model based on (a) $\geq$70% atypical epithelioid cells, (b) $>$2 mitotic

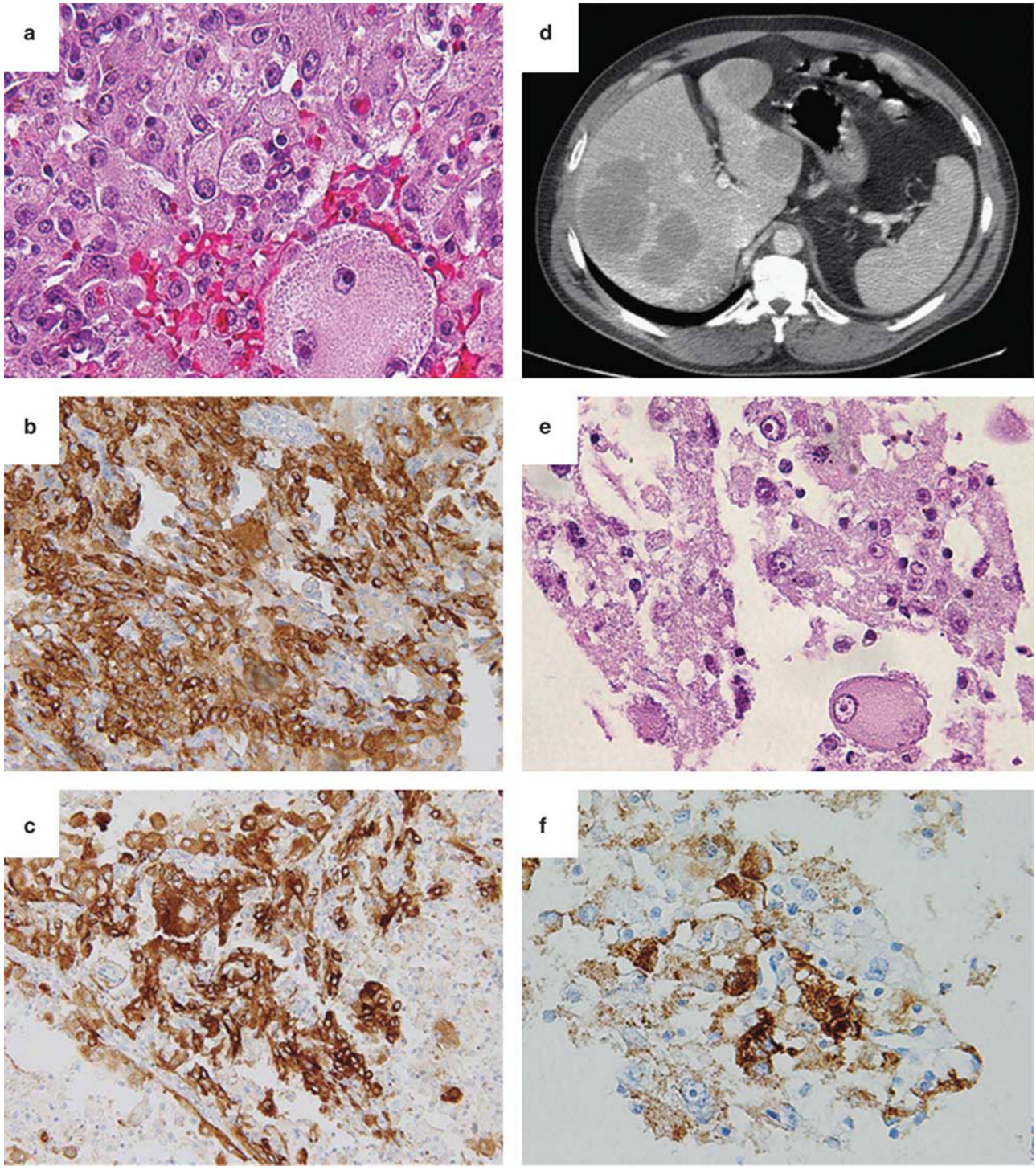

Figure 5 Renal epithelioid angiomyolipoma (AML) with liver metastasis. (**a**) Renal epithelioid-AML (Case 6) with ganglion-like epithelial cells. (**b**) Immunohistochemical stain for A103 in renal tumor cells. (**c**) Immunostain for HMB45 in renal tumor cells, (**d**) multiple liver metastatic nodules on CT scan. (**e**) FNA of the liver mass exhibiting tumor cells with similar morphology as seen in the primary renal tumor. Note the ganglion-like cells, enlarged vesicular nuclei, and prominent nucleoli. (**f**) Immunohistochemical stain for HMB45 in tumor cells from liver FNA.

figures/10 HPF, (c) atypical mitoses, and (d) necrosis; presence of three or more of the features was highly associated with malignant behavior. In our series of consecutively resected specimens, the only one of 20 epithelioid-AMLs that showed a malignant behavior did show some of these reported aggressive features, including large size (19 cm), 100% epithelioid histology composed exclusively

of atypical cells, and extensive necrosis. It also contained multinucleated tumor giant cells. However, the tumor did not show any identifiable mitotic figures, renal vein or peri-renal/sinus fat invasion. More importantly, there were other tumors among our epithelioid-AMLs that contained three or more of the above-mentioned features in variable combinations, but none of these showed evidence of aggressive clinical behavior at the last follow-up. Therefore, it is highly likely that the type of cases included in the studies discussed—primarily consultation cases—is influencing the results. It is a standard of care that morphologically atypical lesions are sent for second opinion. Tumors with manifested aggressive clinical behavior are also usually referred to tertiary centers for further care. The adverse clinical behavior reported in the Brimo *et al*[12] and Nese *et al*[13] studies could easily have been influenced by either one of these factors.

It is remarkable that 30% of cases reported by Nese *et al*[13] had metastatic disease at presentation. We indeed have seen several cases of malignant AML in our consultation practices and have also seen cases that came to our institutions to seek specialized care following disease progression. The goal of our study was not to refute the fact that epithelioid-AML can behave in a malignant fashion, but to investigate the true incidence of this variant and its true biological behavior. Using the specified selection criteria, we find that both the incidence of epithelioid-AML among all consecutively resected AMLs, as well as disease progression among such cases with a long follow-up is quite low. It is certain that had we included consultation cases and cases referred to our institutions for follow-up care, the incidence of malignancy would have been much higher. However, our study provides a more accurate incidence, as well as clinical behavior of epithelioid-AML and may help treating physicians in their follow-up conversations with patients who have undergone resection of tumors pathologically reported as epithelioid-AML.

An overwhelming majority of the cases that do not have metastasis at the time of presentation have been reported to develop metastases within the first 29 months of the primary diagnosis.[12,13] While 3 of our 20 cases had clinical follow-up of less than 1 year, in 4 it ranged from 11.5–27.5 months and in the remaining 13 cases it was from 33–356 months. The paucity of adverse outcomes (only 1 of 20 developing liver metastasis) even over long follow-up periods among most of our cases supports the contention that overall routinely resected epithelioid-AMLs have a low malignant potential.

When epithelioid component predominates and nuclear atypia is prominent, these tumors can be erroneously diagnosed as renal cell carcinoma or sarcoma.[7,18] Proper sampling of the tumor and a clear understanding of the differential diagnosis of such lesions is helpful in rendering the proper diagnosis. It may be necessary to perform immunohistochemical studies to confirm the diagnosis of epithelioid-AML.[19,20] These tumors are usually immunoreactive for one or more melanocytic markers, such as HMB45, A103, and MiTF although staining can be focal. They often express smooth muscle markers, particularly SMA and less commonly desmin. The absence of staining for S-100 protein can help distinguish an E-AML from melanoma.

Morphologic and genetic studies have shown that renal AML is closely related to the PEComa tumor family, as well as with the tuberous sclerosis complex (TSC) by demonstrating loss of heterozygosity of the TSC2 locus on chromosome 16p.[17,21,22] The PEComa family includes renal and hepatic AMLs, lymphangiomyomatosis, clear cell 'sugar' tumor of the lung, and a group of similar lesions seen at other sites.[23] Cysts and multiple AMLs are the most common renal manifestation in TSC.[24,25] In our series, only three cases (#1, 2, and 16) had other concurrent renal tumors. In two of these, one additional classical AML each was present; however, no evidence of tuberous sclerosis syndrome was documented in these two. In the third case, the patient had documented TSC and multiple renal nodules by imaging studies. The 1-cm epithelioid-AML was the only nodule that was excised.

Recent studies have shown that some targeted therapeutic agents against mTOR molecules, such as sirolimus/rapamycin can be used to treat TSC-associated renal AMLs.[17,26–28] Therefore, the correct diagnosis of renal epithelioid-AML can potentially direct the clinicians, particularly in the patients with extensive disease, to a more effective chemotherapy. The one patient in our series with liver metastasis is presently undergoing treatment with sirolimus, an mTOR inhibitor.

In summary, even though some epithelioid-AML can exhibit malignant behavior as evidenced by local recurrence and/or distant metastasis, the proportion of AMLs that fall in this category is quite small (4.6% in this series), if one applies the 2004 WHO criteria and limits the designation to those with no $<80\%$ epithelioid histology. This is in spite of the fact that as three large institutions, and in particular because MSKCC is a major cancer center, we are potentially more likely to receive more unusual cases. Among consecutive resected epithelioid-AMLs, the incidence of malignant behavior is quite low (5.0%), although this fact requires further confirmation by other large studies. It is also interesting to note that despite the presence of atypical morphology, the mitotic activity and the presence of atypical mitotic figures is low in the majority of these tumors, which may reflect the mostly benign clinical behavior of these tumors as reported by Aydin *et al*[11] and as supported by us in this series of consecutively resected specimens.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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