Epithelioid Leiomyosarcoma of the Uterus

Modern Outcome-based Appraisal of Diagnostic Criteria in a Large Institutional Series

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Abstract: Epithelioid leiomyosarcoma of the uterus is rare and poorly understood. Herein, we characterize a large institutional series of epithelioid leiomyosarcomas aiming to define outcome-determinant diagnostic pathologic features. We also retrieved epithelioid smooth muscle tumors of unknown malignant potential and evaluated a consecutive cohort of leiomyomas for epithelioid subtypes. Of a total of 1177 uterine leiomyosarcomas, 81 (7%) were categorized as epithelioid after review. Epithelioid leiomyosarcoma was strictly defined as having round to polygonal cells with visible pink cytoplasm and round to ovoid nuclei in $\geq 50\%$ of the tumor volume. Average age was 55 years (range: 26 to 81 y). Median tumor size was 11 cm; tumor was >5 cm in 93% of subjects; 47% were stage 1 at presentation. An infiltrative tumor border was observed, grossly and/or microscopically, in 89% of cases; necrosis was noted in 80%, and vascular invasion in 47%. Mitotic count in 2.4 mm^2 (totalling 10 high-power fields, each field 0.55 mm in diameter) ranged from 3 to 100 (median: 26). All cases had moderate, severe or highly pleomorphic atypia. All cases had 2 or 3 of the following: necrosis, at least moderate atypia and ≥ 4 mitoses in 2.4 mm^2. Immunohistochemistry revealed frequent expression of smooth muscle markers including SMA (96%), desmin (95%), and caldesmon (81%). HMB45 and Melan-A were negative in 92% and 100% of cases, respectively. Estrogen and progesterone receptors were expressed by 65% and 54% of tumors, respectively. Follow-up information was available in 68 subjects (median: 23 mo, range: 1 to 254); cancer-related death occurred in 63%, and an additional 15% had recurrent or metastatic disease at last follow-up. Disease-specific survival was shorter in epithelioid leiomyosarcoma patients (median: 44 mo; 35% at 5-y) than in a matched cohort of non-epithelioid leiomyosarcoma (median: 55 mo; 46% at 5-y) ($P=0.03$). Three epithelioid smooth muscle tumors of unknown malignant potential were evaluated, all <5 cm in size and with atypia and/or irregular borders but mitotic count below the threshold for malignancy. Two of these had follow-up available, which was uneventful. Of 142 consecutive leiomyomas assessed, none had epithelioid morphology as defined. Epithelioid leiomyosarcoma is an aggressive neoplasm, sometimes with a remarkably low mitotic count. In the setting of an epithelioid smooth muscle tumor of the uterus, we postulate that the diagnosis of malignancy is made in the presence of ≥ 2 of the following: moderate or severe atypia, ≥ 4 mitoses/2.4 mm^2 and tumor cell necrosis. In their absence, the finding of tumor size ≥ 5 cm, vascular invasion, infiltrative edges or atypical mitoses should be treated with caution, and designation as of at least uncertain malignant potential is warranted.

Key Words: leiomyosarcoma, epithelioid, perivascular epithelioid cell tumor, uterus cancer, uterus neoplasm

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The World Health Organization classification of tumors of female genital organs recognizes 3 types of leiomyosarcoma: conventional (spindle cell), myxoid, and epithelioid. Conventional leiomyosarcoma is by far the most frequent. Myxoid leiomyosarcoma is rare but has been the subject of extensive research in recent years. First, the recognition of its subtle diagnostic features and the value of assessing the tumor border has led to more specific criteria for its diagnosis.[1] Moreover, mounting evidence has shown that the differential diagnosis of myxoid leiomyosarcoma is wide, now to include inflammatory myofibroblastic tumor and high-grade uterine sarcoma with *ZC3H7B-BCOR* fusion or *BCOR* internal tandem duplications.[2–4] The role of selected ancillary tools in this differential has also been established, including ALK, BCOR, p53, and p16 immunohistochemistry as well as molecular testing for *BCOR* and *PLAG1* rearrangements.[5–8]

Epithelioid leiomyosarcoma, in contrast, remains an elusive and poorly understood category of uterine smooth muscle neoplasia. Initial characterizations of this tumor, mostly on series published only in abstract form, highlighted

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an aggressive outcome even in lesions with only one worrisome feature such as tumor necrosis and severe nuclear atypia, as well as those with mitotic counts as low as 3 mitoses in 10 high-power fields (HPFs).[9–11] Based on this literature, the 5th edition of the World Health Organization (WHO) Classification of Female Genital Tumours currently recommends a diagnosis of epithelioid leiomyosarcoma if one or more of worrisome features are present: moderate to severe atypia, tumor cell necrosis or $\geq$1.6 mitoses per mm^2.[12] A modern review of these and other criteria is needed to validate their association with outcome, and therefore their role in the diagnosis of malignancy. In addition, an appraisal of the traditional pathologic criteria in light of a modern differential diagnosis is required. This specifically pertains to uterine perivascular epithelioid cell tumor (PEComa), a mimicker of epithelioid leiomyosarcoma which characterization has been refined in the last decade.[13–16] Aiming to address these knowledge gaps, we describe the clinical and pathologic characteristics of a large institutional series of epithelioid leiomyosarcoma.

MATERIALS AND METHODS

This study was approved by the Institutional Research Board at Brigham and Women's Hospital.

Case Selection and Review

All cases with an initial diagnosis of uterine leiomyosarcoma between July 1989 and April 2020 at Brigham and Women's Hospital, primarily or in consultation and with available archival material, were reviewed. Slides were reviewed initially by 1 gynecologic pathologist (D.B.C.), who assessed microscopic features and identified epithelioid, spindle, myxoid, and pleomorphic morphology in each case. Those identified as having epithelioid and/or pleomorphic components were then reviewed by a second gynecologic pathologist (C.P.-H.). Tumors identified as showing epithelioid cell morphology in at least 50% of the tumor volume by both reviewers were included. Epithelioid morphology was strictly defined as cells with round or polygonal shape, visible pink cytoplasm, and round to ovoid nuclei. Pseudo-epithelioid appearance due to cross-sectioning of smooth muscle fascicles was excluded from this appraisal and from the quantification of the true epithelioid population. Pseudo-epithelioid appearance was considered when an "epithelioid" population formed a discreet bundle of cells surrounded by similarly sized longitudinally sectioned fascicles composed of spindle cells.

In order to identify equivalent cases of indolent epithelioid smooth muscle neoplasia, our search included cases of epithelioid smooth muscle tumor of uncertain malignant potential (eSTUMP) during the same time period. In addition, cases with a diagnosis of leiomyoma by one of the authors (C.P.-H.) between July 2020 and March 2021 were reviewed. A diagnosis of epithelioid leiomyoma was assigned if no malignant features were identified in a tumor with at least 50% epithelioid morphology.

Histopathologic features were assessed on all microscopic slides (median: 4 slides per case, range: 1 to 26), including confirmatory features of malignancy, as follows:

(1) Nuclear atypia, defined using the Broders 4-tier system as follows: 1+ (mild atypia with uniform nuclei, no more than 2-fold larger than a normal myometrial nucleus); 2+ (moderate atypia with nuclear size exceeding 2-fold of a normal myometrial nucleus, but with only subtle nuclear variation); 3+ (severe atypia retaining overt smooth muscle differentiation and only scattered pleomorphic nuclei) and 4+ (diffusely and highly pleomorphic nuclei).
(2) Mitotic count using a ×400 magnification objective (field diameter 0.55 mm). Mitoses were counted in at least 50 fields in each case, and the highest count in 10 of the HPFs evaluated (corresponding to 2.4 mm^2) was recorded. A mitotic figure was defined as a nuclear structure with well-formed chromatids appreciable at high power magnification (either clumped or clearly separated) in a cell without a visible nuclear membrane and without a hyper-eosinophilic cytoplasm. The presence of atypical (tripolar or multipolar) mitoses was also recorded.
(3) Tumor cell necrosis, defined as sharply outlined areas of devitalized tumor, usually with irregular and convoluted (geographic) demarcation from the viable tissue, and scored as present or absent.
(4) Tumor border, defined as the shape of the interface with the surrounding uterine wall, and scored as circumscribed, microscopically infiltrative, or grossly/diffusely infiltrative.

If present, the amount of a conventional spindle cell component was also recorded as a percentage of the tumor volume. Other characteristics recorded included the presence of cells with clear granular cytoplasm, presence of perivascular tumor cell aggregation (defined as tumor cellular density higher around vessels than in the background), and lymphovascular space invasion. Tumor size and description of the macroscopic border were obtained from surgical pathology reports. Available clinical information was documented including patient age, stage at time of initial surgery as per the 2018 International Federation of Obstetrics and Gynecology (FIGO) uterine sarcoma staging system,[17] documented local or distant recurrence, date of last follow-up and status at last follow-up.

Immunohistochemistry Studies

Immunohistochemistry was evaluated in cases with either archival immunohistochemical slides available or with remaining paraffin-embedded tissue for novel immunohistochemistry testing. The panel chosen for review included the following antigens: smooth muscle actin (Sigma, clone 1A4), desmin (Sigma, clone DEU-10), h-caldesmon (Dako, clone h-CD), HMB45 (Dako), Melan-A (Dako, clone A103), Cathepsin-K (Abcam, clone 3F9), BRG1/SMARCA4 (Abcam, clone EPR3912), INI1/SMARCB1 (BD Bioscience, clone 25), fumarate hydratase (Santa Cruz, clone J-13), EMA (Dako, clone E29),

Pan-cytokeratin (Dako, clone MNF116) and AE1/AE3 (Dako). Stains were interpreted in terms of intensity and distribution. The predominant intensity of staining was scored as 0 = absent, 1+ = weak, 2+ = moderate, 3 + = strong; distribution was recorded as percentage of positive tumor cells.

Molecular Analysis

Next-generation sequencing and cytogenetics results were retrieved when available. When performed, formalin-fixed, paraffin-embedded tissue was processed at the Center for Advanced Molecular Diagnostics at Brigham and Women's Hospital (Boston, MA). Unstained 4-μm formalin-fixed paraffin-embedded tissue sections of tumor were manually scraped, and DNA was isolated using a commercially available kit (Qiagen, Valencia, CA) following the manufacturer's instructions. Paired normal tissue was not analyzed. DNA was quantified (PicoGreen) and hybrid capture libraries were prepared following previously published protocols.[18,19] Sheared DNA was hybridized to a set of custom-designed capture probes (Agilent SureSelect) targeting the complete exonic regions of 447 cancer genes and 191 intronic regions across 60 genes for the evaluation of structural rearrangements (OncoPanel). Sequencing was performed using Illumina HiSeq. 2500. Data were analyzed by an internally developed bioinformatics pipeline composed of reconfigured publicly available tools and internally developed algorithms (VisCap Cancer, Phaser, BreaKmer).[18] Manual inspection of identified alterations included cross-reference with the Catalogue of Somatic Mutations in Cancer (COSMIC) (https://cancer.sanger.ac.uk/cosmic) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) databases.

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Numerical variables were compared using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using the Fisher exact test. P-values <0.05 were considered statistically significant, and all P-values were 2-sided. The primary outcome measure was disease-specific survival, defined as the interval from first pathologic diagnosis to death from leiomyosarcoma. Patients dying of other causes (n = 1) or alive at last follow-up were censored. For purposes of comparison, survival of patients with epithelioid leiomyosarcoma was compared with survival of an institutional cohort of nonepithelioid leiomyosarcomas (191

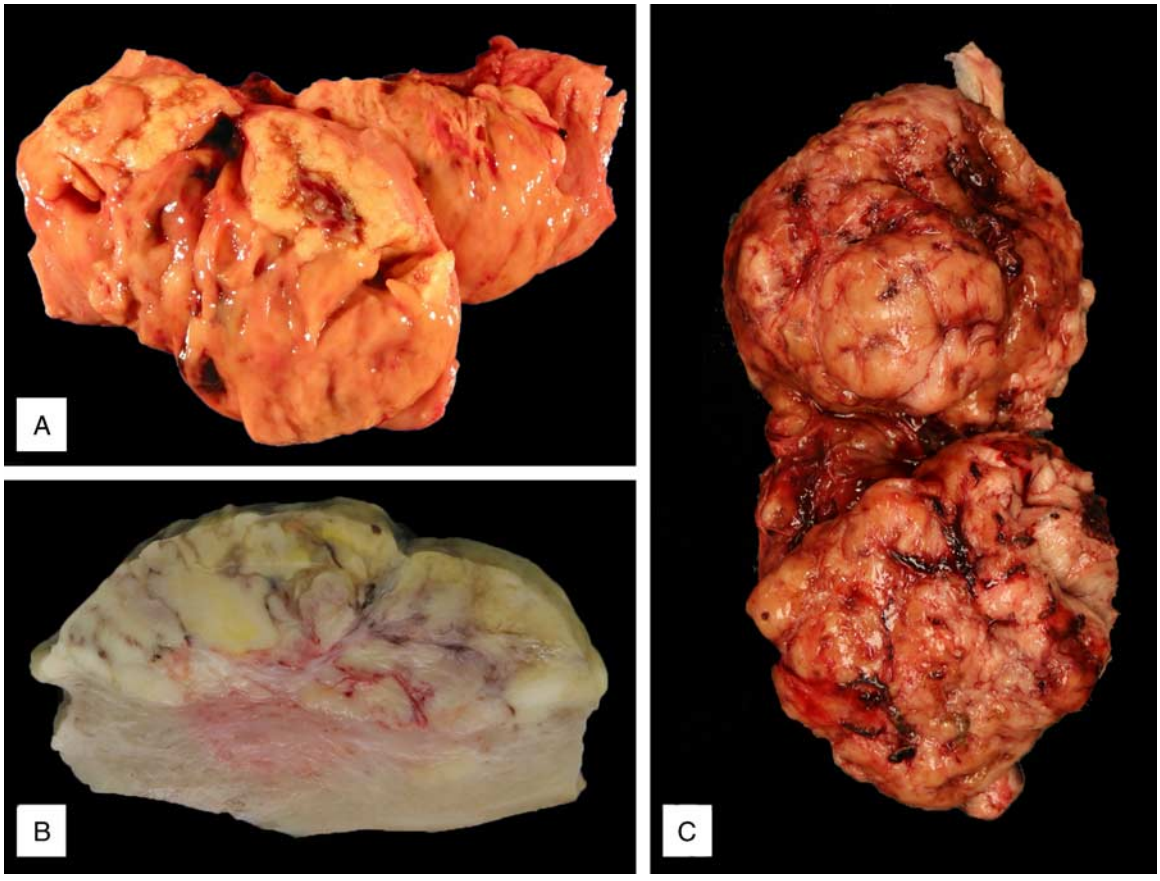

FIGURE 1. Epithelioid leiomyosarcoma, macroscopic appearance. Soft and fleshy tan tumor with areas of necrosis and central cavitation (A). The lesion usually has an irregular, infiltrative tumor interface with the surrounding myometrium (B). Most tumors in this category are larger than 5 cm; the cut surface is heterogeneous with areas of hemorrhage (C).

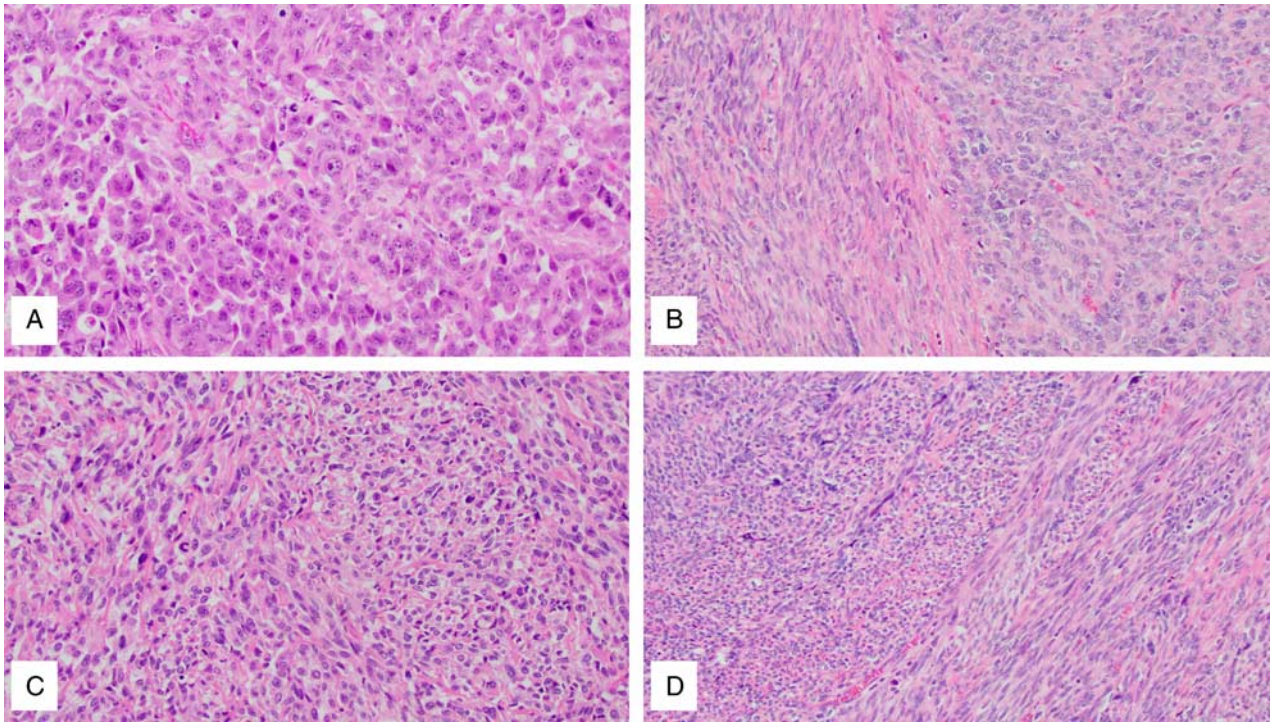

FIGURE 2. Epithelioid leiomyosarcoma. Epithelioid morphology is defined as tumor cells with polygonal or round eosinophilic cytoplasm and round to ovoid nuclei (A). Some tumors are entirely epithelioid, whereas others have a minor (< 50%) spindle cell component. The latter can be seen as discreet areas of fascicular growth (B) or as fusiform cells intermixed with the epithelioid population (C). Pseudoepithelioid appearance in a conventional leiomyosarcoma is given by cross-sectioned fascicles in which the cells appear round (D); these cross-sectioned bundles are small and of similar size compared with the adjacent longitudinally cut bundles (compare with the more expansile and nonbundled appearance of the epithelioid cells in B). Pseudoepithelioid change should be disregarded.

conventional spindled and 18 myxoid) diagnosed during the same timeframe. Survival analysis was performed with the Kaplan-Meier method and survival curves were compared using the log rank test, with multiple comparisons corrected by the Tukey method. Cox proportional hazards regression was used for univariate modeling of continuous variables, calculation of univariate hazard ratios, and multivariate analyses. The assumptions of Cox modeling were satisfied.[20]

RESULTS

A total of 1177 patients with uterine leiomyosarcoma were identified. Of these, 81 (7%) met the definition of epithelioid leiomyosarcoma and constitute the study group. Our search also retrieved 3 eSTUMPs. Of a total of 142 leiomyomas reviewed, none were categorized as epithelioid.

Uterine Epithelioid Leiomyosarcomas (n = 81)

Clinical and Pathologic Characteristics

Information collected is available in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/PAS/B232). Average age was 55 (median: 53, range: 26 to 81) years. Tumor size was available in 73 cases and was 11.6 cm in average (median: 11 cm, range: 3.5 to 26 cm). Notably, tumor size was 5 cm or greater in 68/73 (93%) lesions. The tumor was often described as soft and heterogeneous with frequent hemorrhage and necrosis. Illustrative macroscopic features are shown in Figure 1.

Pathologic features are depicted in Figures 2–4. The epithelioid cell component in each case ranged between 50% and 100% of the entire tumor volume (mean: 81%, median: 88%). Sixty-four tumors (79%) had an epithelioid morphology in ≥ 70% of the cells. Perivascular tumor cell aggregation was not observed in any tumor. Thirteen (16%) tumors showed focal and 2 (3%) showed > 50% clear cell change. Nuclear atypia 2+, 3+, or 4+ was identified in all tumors with the following distribution: 2+ in 22 (27%), 3+ in 30 (37%), and 4+ in 29 (36%). None of the epithelioid leiomyosarcomas showed mild atypia (Broders score 1).

The mitotic count per 2.4 mm^2 (10 HPFs) was in average 35, with a median 26 and range from 3 to 100 mitoses. Most tumors had at least 10 mitoses per 2.4 mm^2 (69 cases, 85%). Eleven additional cases (14%) had a maximum mitotic count between 4 and 9 mitoses per 2.4 mm^2, and only 1 (1%) had 3 mitoses per 2.4 mm^2 (this case had 3+ atypia and tumor cell necrosis). Atypical mitoses were found in 44 cases (54%).

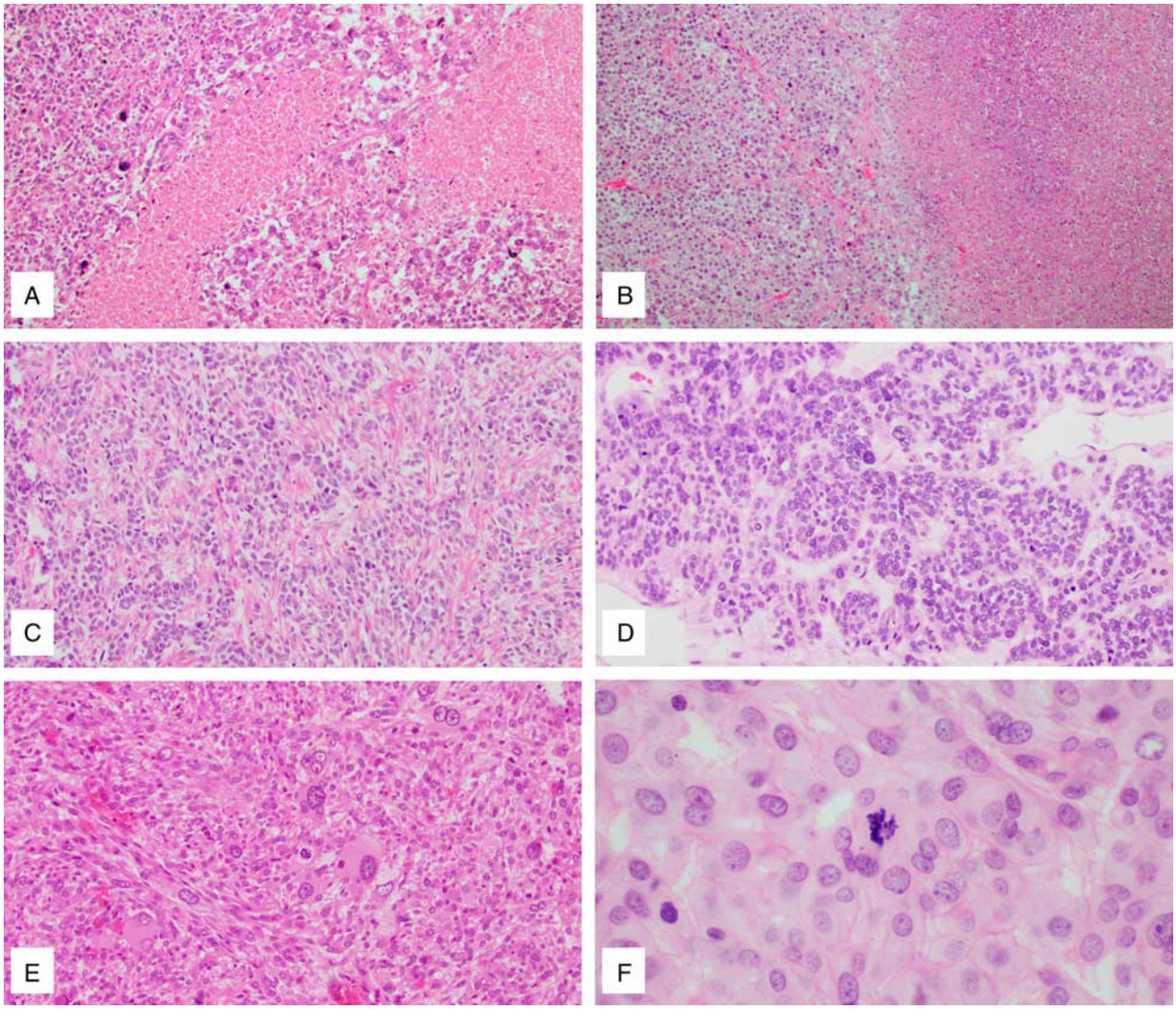

FIGURE 3. Epithelioid leiomyosarcoma. Tumor cell necrosis is characterized by a sharp interface between viable and necrotic tissue (A, B); the epithelioid appearance of the tumor cells is often more pronounced around areas of necrosis. Nuclear atypia can be moderate/2+ (C), severe/3+ (D) or pleomorphic/4+ (E). Mitoses can be focal and <10 in 2.4 mm^2 (F).

Tumor cell necrosis was a frequent finding, observed in 65 (80%) of tumors. The viable tumor near necrosis often displayed overt epithelioid appearance; however, epithelioid morphology was not restricted to those areas. Indeed, the percentage of epithelioid component was similar in tumors with necrosis (mean: 81%, median: 85%) than in those without any necrosis (mean: 83%, median: 90%). Lymphovascular space invasion was present in 38 (47%) lesions. Of 64 tumors in which the tumor border was assessable, 40 (63%) were grossly and/or extensively infiltrative. Of the remaining, 17 (26%) had microscopic infiltration into the surrounding myometrium, and only 7 (11%) were well-circumscribed.

Immunohistochemistry

Immunohistochemical results are available in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/PAS/B232). Smooth muscle actin was positive in 65/68 (96%), desmin in 72/76 (95%), and caldesmon in 52/64 (81%) of cases in which immunohistochemistry was performed. SMA staining was strong (3+) in 60 tumors, moderate (2+) in 4, and weak (1+) in 1, with distribution averaging 60% of tumor cells. Desmin was strong (3+) in 67 tumors and moderate (2+) in 5, with distribution averaging 50% of tumor cells. Caldesmon was strong (3+) in 48 tumors, moderate (2+) in 3, and weak (1+) in 1, with distribution averaging 35% of tumor cells. Conversely, 49/53 (92%), 42/42 (100%), 7/8 (88%), and 2/2 (100%) cases with either archival or prospectively performed stains were negative for HMB45, Melan-A, PNL2, and MiTF, respectively. HMB45 was positive in 4 tumors, always with weak to moderate staining limited to 1% to 2% of cells. One case showed weak PNL2 staining in <1% of cells. Twenty-six tumors were stained for Cathepsin-K, of which

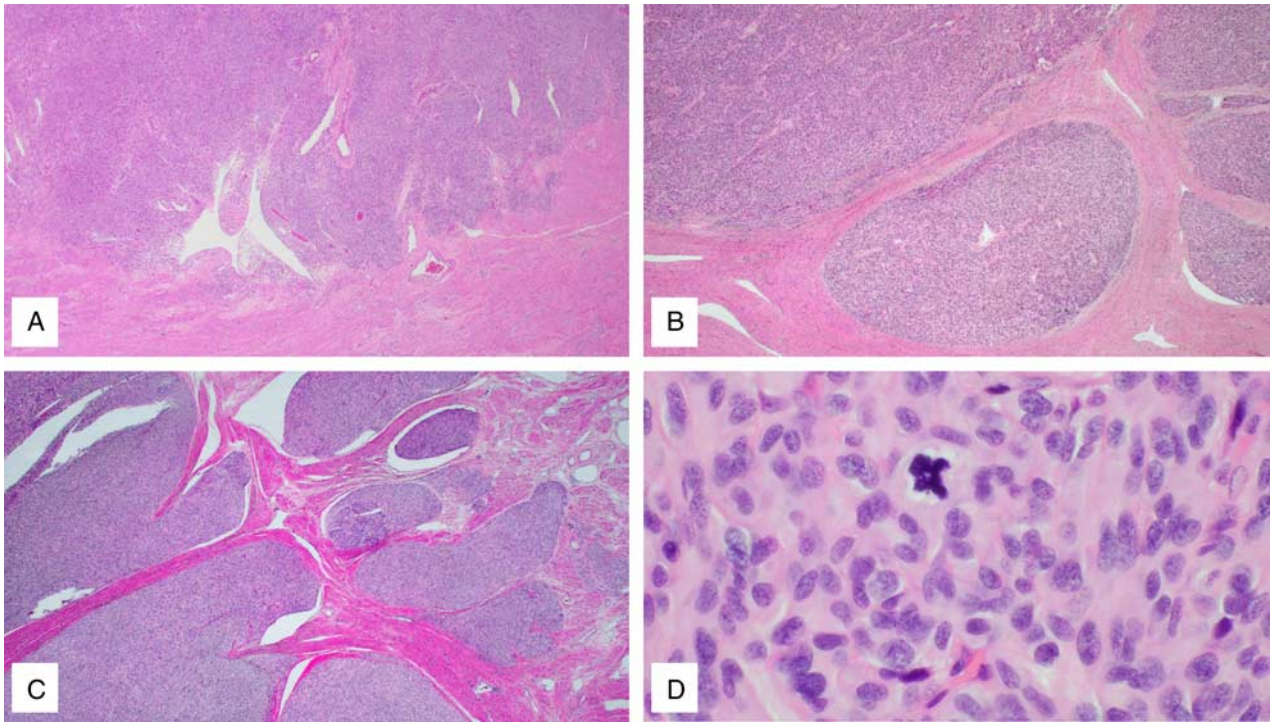

FIGURE 4. Additional pathologic findings in epithelioid leiomyosarcoma. The tumor edge is often infiltrative. Such finding can be subtle and better seen microscopically as indented or markedly irregular tumor borders (A) or extensive in the form of multiple discontinuous tumor masses (B), sometimes with associated vascular space invasion (C). Atypical mitotic figures are also commonly observed (D).

19 (73%) were positive (strong in 5, moderate in 4, weak in 3, staining 1% to 50% [mean, 20%]). All PEComa markers were negative in the 15 tumors with focal clear cell change (see above). Estrogen and progesterone receptors were positive in 34/52 (65%) and 28/52 (54%), respectively. Percentage of positive cells ranged from 2% to 100% (mean: 70%; median: 80%) for estrogen receptor, and from 3% to 100% (mean: 65%; median: 80%) for progesterone receptor. Fumarate hydratase showed normal (retained) cytoplasmic expression in 62/62 (100%) tumors tested. SMARCA4 and SMARCB1 showed retained nuclear expression in 20/20 (100%) tumors tested.

Molecular Analysis

Comprehensive sequencing analysis was completed in 9 tumors. The most commonly affected genes were *ATRX* (4/9, pathogenic single nucleotide variants in 3 and bi-allelic deletion in 1), *TP53* (4/9, pathogenic variants in 2 and bi-allelic deletion in 2), *PTEN* (2/9, bi-allelic deletion) and *CDKN2A* (2/9, bi-allelic deletion). None of the cases analyzed harbored *TFE3* amplification or *TSC1/2* mutations, with the exception of 1 case. This tumor had a *TSC2* variant of unknown significance (as per ClinVAR, not reported in COSMIC). The lesion was purely epithelioid with no clear cytoplasmic change; it was negative for HMB45 and Melan-A, and positive for SMA, desmin and caldesmon). Cytogenetic analysis, successfully completed in 7 tumors, showed a complex karyotype with multiple chromosomal losses and gains in 3 cases, single alterations in 2 (loss of chromosome X in 1, t(4;6)(q31;q15) in another), and normal karyotype in 2 cases.

Clinical Outcome Data

Follow-up information was available in 68 (84%) epithelioid leiomyosarcoma patients. Follow-up period ranged from 1 to 254 (average: 45, median: 23) months. At time of last follow-up, 43 (63%) subjects had died of disease, and 10 (15%) were alive with recurrent or metastatic disease. One patient had died of breast cancer 9 months after diagnosis of leiomyosarcoma. Fourteen patients (21%) were alive with no evidence of disease, including 10 (15%) with follow-up beyond the immediate postoperative period (range, 11 to 254 mo). Disease-specific survival was shorter in epithelioid leiomyosarcoma patients (median: 44 mo; 5-y, 35%) than in patients with nonepithelioid leiomyosarcoma (median: 55 mo; 5-y, 46%) ($P = 0.03$) (Fig. 5).

Combination of features used in conventional and epithelioid uterine leiomyosarcoma, namely moderate or severe atypia (Broders grade 2 or higher), tumor cell necrosis and mitotic count of either ≥ 10 (conventional) or ≥ 4 (epithelioid) per 2.4 mm^2, is shown in Table 1. All cases had at least 2 worrisome features indicative of malignancy as defined for epithelioid smooth muscle tumors by the WHO Classification. Conversely, if using a cut-off of 10 mitoses per 2.4 mm^2, 75 cases had 2 or 3 features, while 6 tumors had atypia as the only qualifying feature of

malignancy (and had 4-9 mitoses per 2.4 mm^2). Of these 6 cases, adverse outcome was documented in 3 of 4 patients with follow-up information available: 2 patients died of disease at 11 and 55 months each, 1 developed recurrence 35 months after initial diagnosis, and 1 was alive with no evidence of disease at 97 months of surveillance. In other words, most of these patients had poor outcome despite having a proliferative index below the threshold for conventional (spindle cell) leiomyosarcoma.

Tables 2 and 3 show the correlation between survival and pathologic variables. On univariate analyses, shorter disease-specific survival was significantly associated with stage III or IV disease, larger size of primary tumor, mitotic activity ≥ 10 per 2.4 mm^2, and lymphovascular invasion. In a multivariate model, tumor size, mitotic activity, and lymphovascular invasion, but not tumor stage, were independently associated with survival.

Compared with nonepithelioid tumors, epithelioid tumors were significantly more likely to receive adjuvant therapy (52% vs. 35%, $P = 0.016$) and to show grade 4 nuclear atypia (36% vs. 25%, $P = 0.048$), coagulative necrosis (81% vs. 70%, $P = 0.049$), and lymphovascular invasion (56% vs. 39%, $P = 0.017$). There was no significant difference between epithelioid and nonepithelioid tumors in age ($P = 0.96$), stage ($P = 0.52$), size ($P = 0.44$), mitotic count ($P = 0.27$), or atypical mitoses ($P = 0.60$).

Epithelioid Smooth Muscle Tumors of Uncertain Malignant Potential (n = 3)

Clinical and pathologic characteristics of the 3 eSTUMPs are listed in Table 4. All 3 tumors were < 5 cm in size and were confined to the uterus (FIGO stage IA). They were classified eSTUMP based on the presence of moderate atypia *or* mildly elevated mitotic count. In addition, 2 tumors had a microscopically irregular border. Tumor cell necrosis was not identified in this group. All 3 cases expressed SMA and desmin (3+ staining in 10% to 50% of cells); 1 of 2 cases stained with caldesmon was positive (3+ staining). Follow-up information was available in 2 subjects; both were alive with no evidence of disease at 19 and 155 months, respectively.

DISCUSSION

Leiomyosarcoma is the most common malignant mesenchymal neoplasm of the uterus. Recurrence-free, overall and disease-specific survival in patients with this disease are mostly dependent on FIGO stage, although other factors such as age, race, tumor size, tumor grade, mitotic count, and lymphovascular invasion have been shown to be prognostic.[21–23] To our knowledge, our series constitutes the largest cohort of patients with uterine epithelioid leiomyosarcoma published to date. This variant of smooth muscle neoplasia is rare, representing 2% to 7% of all leiomyosarcomas based on our series and others.[24] We confirm that this tumor type is aggressive, with shorter median and lower 5-year disease-specific survival compared with an institutionally matched cohort of nonepithelioid leiomyosarcomas. Our findings show the prevalence of several histopathologic characteristics and their association with patient outcome, thus serving as the basis to validate histologic criteria for the diagnosis of this tumor type.

The criteria for the diagnosis of epithelioid uterine smooth muscle neoplasia outlined by the current World Health Organization classification are based on series by Kurman and Norris,[25] Prayson et al,[9] Oliva et al,[10] and Atkins et al.[11] Kurman and Norris[25] described the features of 26 uterine epithelioid smooth muscle tumors, 3 of which had recurrence and/or cancer-related death; they noted that the three recurring tumors had all infiltrative borders, necrosis, lack of hyalinization and lack of clear cells. Prayson and colleagues documented 18 epithelioid smooth muscle tumors, 9 of which had follow-up of 5 to 203 months. While no single histologic feature in their study was predictive of metastatic potential, tumors with aggressive course showed significant nuclear atypia (grade 2 or 3), at least 3 to 4 mitoses in 10 HPFs and/or tumor cell necrosis.[9] The study by Oliva and colleagues included 80 cases; 32 of the 55 patients with > 1 year of follow-up were alive free of disease, whereas 23 had recurrence or cancer-related death. This study assessed for tumor cell necrosis, vascular invasion, significant nuclear pleomorphism, and mitoses of 3 or more in 10 HPFs. Interestingly, clinically malignant behavior was documented in 9%, 42%, 56%, 88%, and 80% of cases with none, 1, 2, 3, or 4 of such features.[10] Atkins and colleagues evaluated 32 epithelioid tumors in patients with at least 2 years of surveillance. Most tumors with tumor cell necrosis (4/5) had poor outcome; as well as those without necrosis but showing significant atypia (4/8) or ≥ 5 mitoses in 10 HPFs (3/4).[11] While it is difficult to compare this evidence as the methodology used is not uniform, salient findings are (1) the uniform documentation of poor clinical outcome even in tumors with subtle morphologic features, and (2) the proliferation index associated with malignancy, which is lower than in conventional uterine leiomyosarcoma. Based on our findings, we propose that the diagnosis of epithelioid leiomyosarcoma requires 2 of 3 worrisome features (instead of just 1, which based on our institutional review is a rare and poorly documented scenario which requires further study).

It is important to note that epithelioid leiomyosarcoma requires the presence of unequivocal epithelioid morphology, that is round to polygonal cells with pink cytoplasm and round to ovoid nuclei comprising most ($\geq 50\%$) of the tumor volume. While this threshold is rather arbitrary, it appears to be accepted to separate epithelioid from spindle cell categories. Based on our series, when an epithelioid component is present it represents most of the tumor volume: in 79% of our cases the epithelioid population represented $\geq 70\%$ of the tumor. In the remaining minority, the epithelioid population was more evenly admixed with a conventional fusiform component. Furthermore, it is critical to separate true epithelioid smooth muscle differentiation from spindle cell tumors with "pseudoepithelioid" appearance, in which the round cell morphology is a result of spindle cell fascicles cut transversally. Of note, the series by Atkins et al[11] included some cases with pseudoepithelioid morphology.

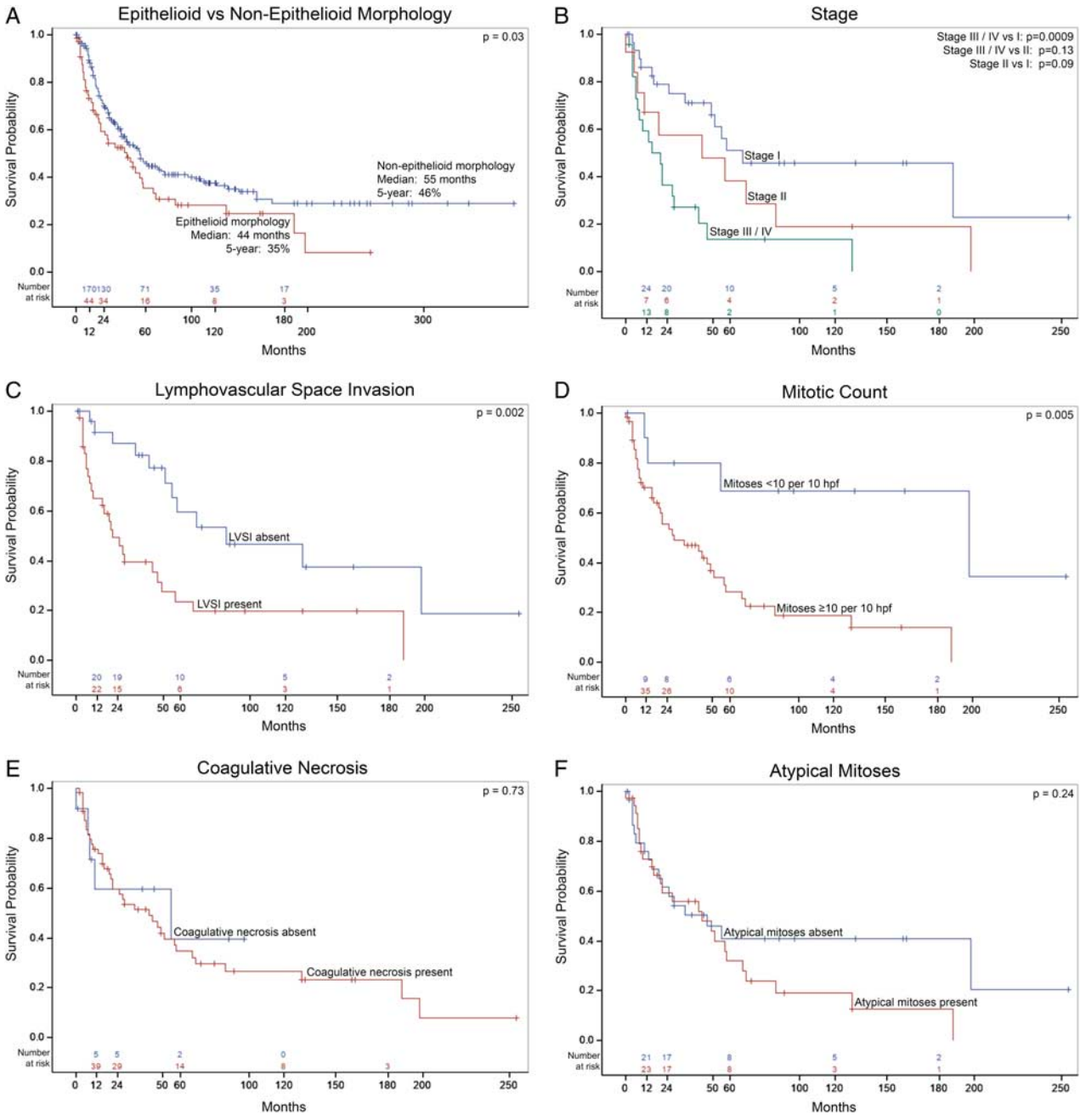

FIGURE 5. Univariate survival analyses, Kaplan-Meier method. Shorter disease-specific survival was significantly associated with epithelioid morphology extrapelvic (stage III/IV) disease lymphovascular space invasion (LVSI) and ≥10 mitoses per 10 high-power fields (field diameter, 0.55 mm) but not with presence of coagulative necrosis or atypical mitoses.

We believe these cases should be classified as conventional leiomyosarcoma; proper sampling and careful microscopic examination should be exercised to identify the fascicular arrangement of the lesion.

Little is known about why tumors of smooth muscle derivation acquire epithelioid morphology. The ultrastructure of epithelioid leiomyosarcoma is characterized by presence of cytoplasmic intermediate filaments, pinocytosis and subplasmalemmal densities, all supportive of smooth muscle differentiation.[26,27] Tumor cells are noncohesive and are separated by a scant collagenous matrix.[26] The intermediate filaments can be parallel to the membrane surface, but also have been described as randomly arrayed[27] which could be implicated in the loss of the elongated shape of smooth muscle cells. Oncocytic change, associated with the presence of numerous mitochondria, has also been described.[28] In this context, an epithelioid morphology could herald loss of differentiation relative to conventional (spindle cell) leiomyosarcoma, a phenomenon that may explain the more aggressive behavior of epithelioid leiomyosarcoma. In

TABLE 1. Distribution of 81 Uterine Epithelioid Leiomyosarcomas in Terms of Presence of Atypia, Necrosis, and Mitotic Count

	Mitotic Count Threshold	
	≥ 10 in 2.4 mm^2	≥ 4 in 2.4 mm^2
Atypia+necrosis+mitoses	60	64
Necrosis+mitoses	0	0
Atypia+necrosis	6	1
Atypia+mitoses	9	15
Atypia only	6	0
Mitoses only	0	0
Necrosis only	0	0
None	0	0
Total	81	81

addition, the epithelioid shape could be related to cellular injury or response to hypoxic or other stress. Tumor cell necrosis was a common finding in our cohort (80% of cases), and we observed that the epithelioid appearance was often conspicuous around areas of cell necrosis. Nonetheless, it is notable that epithelioid change was seen with similar frequency and abundance in tumors without any tumor cell necrosis.

TABLE 3. Multivariate Disease-specific Survival Analysis (n = 68)

	Hazard Ratio (95% CI)	P
Stage	NS	0.15
Size (per cm)	1.15 (1.07-1.24)	0.002
Mitotic count ≥ 10 per 2.4 mm^2	9.1 (1.2-67.7)	0.02
Lymphovascular invasion	3.6 (1.6-8.2)	0.01

CI indicates confidence interval; NS, not significant.

The differential diagnosis of epithelioid leiomyosarcoma includes several entities with epithelioid and round cell morphology. This includes perivascular epithelioid cell tumor (PEComa), uterine tumor resembling ovarian sex cord stromal tumor (UTROSCT), rhabdomyosarcoma, endometrial endometrioid carcinoma with solid (FIGO grade 3) or undifferentiated morphology and undifferentiated uterine sarcoma. PEComa is an important and often challenging differential, as this lesion often has a spindle cell component and smooth muscle marker expression. In the setting of an epithelioid uterine neoplasm, PEComa should always be considered, and

TABLE 2. Univariate Disease-specific Survival Analysis of Clinico-pathologic Variables in Patients With Uterine Epithelioid Leiomyosarcoma and Available Follow-up (n = 68)

	n	Median DSS (mo) (95% CI)	Hazard Ratio	P
Age at diagnosis				0.17
Adjuvant treatment after initial diagnosis				0.1
Administered	29	28 (10-86)	NS	
Not administered	26	51 (34-NR)		
Stage				0.003
I	32	67 (49-NR)	IV vs. I: 3.2 (1.5-7.1) ($P = 0.007$)	
II	13	44 (5-86)	III vs. I: 4.3 (1.6-11.3) ($P = 0.003$)	
III	7	11 (4-NR)	Other pairwise comparisons NS	
IV	16	21 (6-42)		
Tumor size (per cm increment)			HR = 1.139 (1.059-1.225)	0.0003
Percent epithelioid			NS	0.28
Broders grade				0.17
1	0	.	NS	
2	19	40 (13-NR)		
3	26	44 (27-NR)		
4	23	20 (8-58)		
Mitoses (per additional mitotic figure increment)			HR = 1.018 (1.007-1.029)	0.0015
Mitotic count				0.005
≥ 10 mitoses per 2.4 mm^2	57	28 (16-51)	4.8 (1.5-15.9)	
< 10 mitoses per 2.4 mm^2	11	198 (11-NR)		
Atypical mitoses				0.24
Present	35	44 (16-58)	NS	
Not identified	32	47 (15-NR)		
Coagulative necrosis				0.73
Present	56	42 (20-58)	NS	
Not identified	12	55 (7-NR)		
Lymphovascular invasion				0.002
Present	36	21 (9-47)	2.9 (1.4-5.9)	
Not identified	27	86 (51-NR)		
Border				0.4
Circumscribed	6	44 (10-NR)	NS	
Microscopic infiltration	14	69 (8-NR)		
Gross or overt infiltration	36	47 (20-130)		

CI indicates confidence interval; NR, not reached; NS, not significant.

TABLE 4. Clinico-pathologic Variables of Patients With Epithelioid Smooth Muscle Tumor of Uncertain Malignant Potential (n = 3)

Case	Patient Age (y)	Tumor Size (cm)	FIGO Stage	Epithelioid Component (%)	Atypia	Necrosis	Mitotic Count in 10 HPFs	Tumor border	Follow-up Period (mo)	Status at Follow-up
1	50	3.7	IA	95	2+	Absent	1	Focally irregular	155	Alive, no evidence of disease
2	20	4.6	IA	100	2+	Absent	0	Smooth	19	Alive, no evidence of disease
3	28	2.4	IA	80	1+	Absent	3	Focally irregular	Not available	

excluded by looking for clear cell epithelioid morphology (which is rare and focal in epithelioid leiomyosarcoma as shown in our series), perivascular aggregation (not seen in our cohort) and expression of melanocytic markers (which should be strong and correlate with the clear cell epithelioid components). Notably, clear cell change and HMB45 are not unequivocal signs of PEComa, and some authors allow them in epithelioid leiomyosarcoma.[29] We were able to determine the HMB45 and Melan-A status, either through archival material or prospectively, in most of our cases. We acknowledge that in a subset of cases, we were unable to complete such work-up as no additional material was available. To account for this limitation, our review of the histologic material was strict and documented the presence of clear cytoplasm and perivascular tumor aggregation. Moreover, we consider that the immunohistochemistry results in the cases in which it was successfully performed validates our morphologic approach.

Molecular testing can be of value when morphology is ambiguous.[30] The molecular alterations presented in the small subset of cases from our cohort with information available mirror that of previously published literature in uterine leiomyosarcomas, with frequent aberrations in *ATRX*, *TP53*, *CDKN2A*, and *PTEN*.[31] While limited to 9 cases, it is worth noting that none of them harbored pathogenic mutations in *TSC1/2*, which conversely occur in PEComas.[32] Unfortunately, the Oncopanel test does not survey for *TFE3* rearrangements; *TFE3* translocation-associated PEComa typically shows epithelioid clear cell morphology and diffuse melanocytic marker expression,[15] which were not seen in our series. Our sequencing panel does not cover *PGR*; rearrangements involving this gene have been recently described in 6/17 epithelioid leiomyosarcomas.[33] UTROSCT typically shows a variety of patterns typically associated with ovarian sex cord stromal neoplasia including trabecular, insular, solid and glandular, which were not observed in our cohort. While UTROSCT is often positive for smooth muscle markers, expression of ovarian sex cord stromal markers and keratins is also often seen and should suggest this diagnosis. Sex cord-like morphology can arguably occur in epithelioid leiomyosarcoma, as described in one case report[34]; in this case, the sex cord-like areas were positive for desmin, SMA, and WT1 but negative for inhibin, calretinin, and CD10, suggesting morphologic mimicry rather than true sex cord stromal differentiation. UTROSCT is characterized by frequent *NCOA1-3* rearrangements,[35] and molecular testing can be of value in difficult instances.

Epithelioid leiomyosarcoma should be distinguished from rhabdomyosarcoma, which can also show epithelioid cell morphology. The phenomena of rhabdoid morphology and rhabdomyosarcomatous differentiation have been described in epithelioid leiomyosarcoma.[33,36–38] However, in 2 reported cases myoglobin expression was described[36,37] and in another rhabdomyoblastic ultrastructural features were confirmed,[38] raising the possibility of either misdiagnosis or true focal rhabdomyosarcomatous differentiation in epithelioid leiomyosarcoma. Undifferentiated uterine sarcoma should be considered in tumors with severe nuclear atypia or overt pleomorphism. As seen in our series, robust staining for smooth muscle markers is a feature of epithelioid leiomyosarcoma, and such finding would be against an undifferentiated malignancy. Of note, staining was only focal, but strong, in 4 tumors in our series, so careful scrutiny of the stains is necessary. A diagnosis of epithelioid leiomyosarcoma should be favored if there is at least moderate to strong expression of at least 1 muscle marker in the right morphologic context.

The differential diagnosis of epithelioid leiomyosarcoma also includes epithelioid leiomyoma and eSTUMP. Based on our results, we conclude that these 2 latter entities are exceedingly rare. A review of 142 consecutive leiomyomas seen at our institution failed to identify any leiomyoma of epithelioid type. Moreover, during the same time period covered in our search we were only able to confirm 3 eSTUMPs. Remarkably, all 3 cases were < 5 cm in size, whereas 93% of epithelioid leiomyosarcomas studied was 5 cm or greater. As expected, these 3 cases only had either moderate atypia or mitotic count approaching the threshold for epithelioid smooth muscle malignancy. This number of eSTUMPs is very small and outcome data was only available in 2 patients. Nonetheless, epithelioid morphology in STUMP has been associated with adverse outcomes.[39] Based on our findings we propose the following criteria for the classification of epithelioid smooth muscle neoplasia (Fig. 6):

(1) Epithelioid leiomyosarcomas consistently show at least 2 worrisome features for malignancy (including the mitotic count threshold of ≥ 4 per 2.4 mm^2, which is supported by our outcome data). Thus, the diagnosis of epithelioid leiomyosarcoma is warranted if 2 or 3 malignant features are present (mitoses ≥ 4 per 2.4 mm^2, moderate to severe atypia or tumor cell necrosis).
(2) If only one feature is identified, the diagnosis of eSTUMP is justified. As seen in our series, this instance is rare and should be treated with caution. Atypical

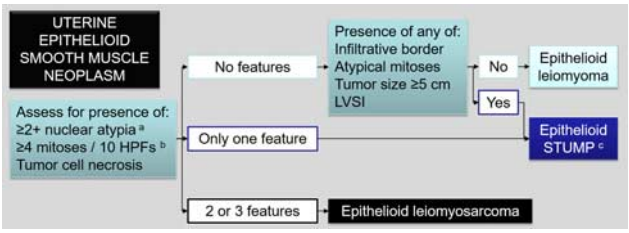

FIGURE 6. Algorithm and proposed criteria for the diagnosis of uterine epithelioid smooth muscle neoplasms. [a]Nuclear atypia is defined as 1+ (uniform nuclei no more than 2-fold larger than a normal myometrial nucleus); 2+ (nuclei >2-fold larger than normal myocyte nucleus, subtle nuclear variation); 3+ (nuclei >2-fold larger than normal myocyte nucleus with significant scattered pleomorphic nuclei); and 4+ (diffusely and highly pleomorphic nuclei). [b]A high-power field (HPF) is defined as one microscopic field under ×400 magnification using an objective 0.55 mm in diameter (area 0.24 mm^2). At least 50 HPFs should be counted, and the highest count in 10 HPFs (equivalent to an area of 2.4 mm^2) is recorded. [c]A diagnosis of epithelioid smooth muscle of uncertain malignant potential (eSTUMP) should be reserved for tumors with only one of the 3 conventional worrisome features (atypia, mitotic count, and necrosis). In addition, presence of tumor size ≥5 cm, infiltrative borders or atypical mitoses should warrant categorization as eSTUMP. These recommendations are based on the very limited experience in these diagnostic scenarios, which preclude optimal risk stratification. LVSI indicates lymphovascular space invasion.

mitoses, tumor size ≥5 cm, lymphovascular space invasion and infiltrative borders are frequent findings in epithelioid leiomyosarcoma, and the presence of any of these characteristics in a lesion without any other worrisome characteristics should also warrant a diagnosis of eSTUMP. The scarce evidence in these scenarios warrants such diagnosis until more evidence is collected. Regarding vascular invasion, one special consideration is intravenous leiomiomatosis. In the largest series of this entity to date, 2 of 28 tumors were categorized as cellular and epithelioid; one of these had extrauterine spread, the other had indolent outcome after 13 years of follow-up.[40] Given the only occasional occurrence of such instance (a bland epithelioid neoplasm with vascular invasion and intrauterine spread) designation as either epithelioid STUMP or epithelioid intravenous leiomiomatosis is prudent as long as the patient receives close and long-term surveillance to monitor for recurrence.

(3) The diagnosis of epithelioid leiomyoma requires a mitotic count of <4 mitoses per 2.4 mm^2 and tumor size <5 cm, as well as absence of moderate to severe atypia, necrosis, atypical mitoses, lymphovascular space invasion, and irregular borders.

The above rationale is limited by the absence of a comparison group. Since we were unable to identify a subset of lesions with few to no worrisome histopathologic features of malignancy, our appraisal of diagnostic criteria for the diagnosis of epithelioid leiomyosarcoma is based on the high prevalence of such features in our cohort and their association with patient outcome. Univariate and multivariate analysis identified tumor size, mitotic activity of ≥10/2.4 mm^2 and lymphovascular invasion as features associated with disease-specific survival. Based on these results, we include these criteria in our algorithmic approach. Nonetheless, we observed that increasing the mitotic count threshold to ≥10/2.4 mm^2 would exclude a subset of cases that behave aggressively, and therefore opted to retain the lower threshold of ≥4 mitoses/2.4 mm^2. Building a comparison group to test these criteria is necessary but may prove difficult as demonstrated by our search for institutional eSTUMPs and epithelioid leiomyomas. It can be argued that true epithelioid smooth muscle tumors are almost never indolent, and therefore should be managed as having malignant potential until better risk models are identified and validated.

In summary, uterine epithelioid leiomyosarcoma is an infrequent but distinct malignant neoplasm with worse biologic behavior compared with conventional (spindle cell) leiomyosarcoma. Most cases have proliferation exceeding 10 mitoses per 2.4 mm^2, although 15% have lower counts. At least moderate nuclear atypia is universally present. Similarly, most epithelioid leiomyosarcomas are 5 cm or more in size and feature infiltration into the surrounding wall, which should alert the pathologist to the possibility of this diagnosis. Based on our findings, we recommend the diagnosis of epithelioid leiomyosarcoma if 2 or 3 worrisome features are present (at least moderate atypia, ≥4 mitoses per 2.4 mm^2, or tumor cell necrosis), and categorization as eSTUMP if only one feature is identified. Atypical mitoses, lymphovascular space invasion, infiltrative tumor borders and size ≥5 cm are also worrisome features as they are frequent in malignant tumors, and their presence (in a tumor that lacks necrosis, atypia and proliferation) warrants classification as eSTUMP. Before assigning a diagnosis of epithelioid leiomyosarcoma, a variety of differential diagnoses should be entertained including PEComa, UTROSCT, rhabdomyosarcoma, undifferentiated sarcoma, and carcinoma. Attention to the cytoplasmic detail and the presence of a conventional spindle smooth muscle component and/or smooth muscle marker positivity is helpful. Moreover, perivascular aggregation is not a feature of epithelioid leiomyosarcoma. Immunohistochemistry for melanocytic and epithelial markers should be negative or at most focal (<5%) in an epithelioid smooth muscle tumor. Achieving the correct diagnosis has important clinical implications, as epithelioid leiomyosarcoma is an aggressive tumor, while PEComa and carcinoma may benefit from targeted therapy. Further investigation is needed to better understand the biology of this infrequent and intriguing category of gynecologic smooth muscle neoplasia.

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