Predicting the Behavior of Perivascular Epithelioid Cell Tumors of the Uterine Corpus

Andres Martin Acosta, MD; Brian P. Adley, MD

• Perivascular epithelioid cell tumors (PEComas) are rare neoplasms that share phenotypic features with angiomyolipomas, clear cell sugar tumors, and lymphangioleiomyomatosis. They presumably represent the neoplastic counterpart of a yet-unidentified perivascular epithelioid cell that expresses smooth muscle and melanocytic immunomarkers. The uterus is the second most common site of origin for perivascular epithelioid cell tumors, after the retroperitoneum. Although most uterine perivascular epithelioid cell tumors are clinically benign and can be cured by a complete surgical excision, there is a subset characterized by both local and distant dissemination. Unfortunately, no single histopathologic or immunohistochemical parameter can accurately predict the clinical behavior of these tumors, which is why the 2012 World Health Organization classification of tumors of the female reproductive organs suggests the use of several criteria to predict the risk of aggressive clinical behavior. Here we review those perivascular epithelioid cell tumors of the uterine corpus with aggressive clinical behavior reported in the literature, and we discuss their most relevant clinical and histopathologic features.

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In the early 1990s it was recognized that renal angiomyolipomas, clear cell sugar tumors, and pulmonary lymphangioleiomyomatosis constitute a group of lesions that have similar histopathologic features and share the expression of melanocytic antigens.[1–3] Because the aforementioned lesions can be entirely or partially composed of clear to eosinophilic epithelioid cells with a tendency to aggregate around vessels, it was proposed that they might originate from a peculiar muscle cell that expresses melanocyte-associated immunomarkers, that is, the perivascular epithelioid cell.[3] The term *PEComa*, as an acronym for perivascular epithelioid cell tumor, was first introduced in 1996 by Zamboni et al,[4] who used it to describe a pancreatic tumor composed of human melanoma black 45 (HMB-45)–positive clear epithelioid cells. Thereafter, neoplasms with an epithelioid cytomorphology and coexpression of smooth muscle and melanocytic immunomarkers have been increasingly reported under the designation of PEComa in a wide variety of anatomic locations. Although PEComas are, in general, rare lesions, the uterus in particular is the second most commonly affected site after the retroperitoneum.[5]

The latest World Health Organization classification of tumors of female reproductive organs[6] defines PEComas of the uterus as mesenchymal tumors typically containing epithelioid cells with clear to eosinophilic, granular cytoplasm demonstrating melanocytic and smooth muscle differentiation by immunohistochemistry. To date, less than 80 cases of uterine PEComa have been reported in the literature.[7] Although the majority of these cases show a good overall prognosis and can be definitively cured by a complete surgical excision, locoregional recurrences, distant metastases, and disease-related deaths do rarely occur. In fact, one of the challenges faced by pathologists is how to predict the biological behavior of PEComas, because no single histopathologic feature is in and of itself a marker of an aggressive biology. For the purposes of this review, we considered as clinically aggressive those PEComas that showed evidence of regional or distant dissemination requiring surgery or chemotherapy.

PATHOGENESIS

The histogenesis of PEComas is still controversial, because a normal counterpart of the perivascular epithelioid cell has not been identified to date.[8] There is a well-established association between PEComas and the tuberous sclerosis complex (TSC), which is caused by mutations in hamartin (*TSC1*, chromosome 9) and tuberin (*TSC2*, chromosome 16) in 27% and 73% of cases, respectively.[8] The protein products of *TSC1* and *TSC2*, together with *TBC1D7* (TBC1 domain family, member 7), form a heterotrimer that promotes the formation of *Rheb*-GDP (guanidine diphosphate–bound Ras homolog enriched in brain protein) from *Rheb*-GTP (guanidine trisphosphate–bound Rheb). The active form of *Rheb*, *Rheb*-GTP, stimulates the formation of mTORC1 (mTOR complex 1), a multiprotein complex composed of mTOR (mammalian target of rapamycin), *Raptor* (regulatory-associated protein of mTOR), *Deptor* (DEP domain–containing mTOR-interacting protein), *mLST8/GβL* (mammalian LST8/G-protein β-subunit–like protein), and *PRAS40* (40-KDa proline-rich AKT substrate).[9] In turn,

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From the Department of Anatomic/Clinical Pathology, University of Illinois at Chicago Hospital and Health Sciences System (Dr Acosta); and the Department of Pathology, Advocate Lutheran General Hospital, Park Ridge, Illinois (Dr Adley).

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Reprints: Andres Martin Acosta, MD, Department of Anatomic/Clinical Pathology, University of Illinois at Chicago Hospital and Health Sciences System, 840 S Wood St, Suite 130 CSN, Chicago, IL 60612 (email: amacosta@uic.edu).

mTORC1 promotes cell growth and metabolism through the activation of ribosomal protein S6 kinase (*S6K*) and eukaryotic translation initiation factor 4E-binding protein (*4E-BP*). Therefore, *TSC1* and *TSC2* act as tumor suppressors by inhibiting mTORC1 through an increase in the concentration of inactive, GDP-bound *Rheb*.

Because of its strategic position within the *mTOR* signaling pathway, mTORC can function as an integrator of both extracellular and intracellular signals. For example, extracellular stimuli that promote cell growth through the *PI3K* (phosphatidylinositol-4,5-bisphosphate 3-kinase) and *MAPK* (mitogen-activated protein kinase) signaling pathways lead to the activation of *Akt* (proto-oncogene Akt) and *ERK* (extracellular signal-regulated kinase) protein kinases, respectively, which results in the inhibition of *TSC1/TSC2/TBC1D7*.[9] In contrast, an increase in the concentration of adenosine monophosphate (AMP) leads to the activation of glycogen synthase kinase 3 (*GSK3*) and AMP-activated protein kinase (*AMPK*), both of which can activate *TSC1/TSC2/TBC1D7*, resulting in decreased cell metabolism and growth.[9] In patients with tuberous sclerosis, the loss of functional TSC proteins prevents the formation of the *TSC1/TSC2/TBC1D7* heterotrimer. As a result, there is a constitutive *Rheb*-GTP–mediated activation of *mTOR*, which leads to increased cell growth and proliferation. Loss of heterozygosity at 16p13, the chromosomal region containing the *TSC2* gene, has been described in sporadic and tuberous sclerosis-associated PEComas.[8] Mutations of *TSC2* have been described in 62% of PEComas overall and in 80% of the PEComa subgroup lacking translocations of the *TFE3* gene, as described below.[10]

Recently, a study[10] of 38 PEComas found that 9 (23%) of them harbored translocations of *TFE3* (transcription factor E3), a member of the microphthalmia transcription factor (*MiTF*) gene family located in the short arm of chromosome X. Although the function of the *MiTF* gene family members as inducers of melanocyte differentiation is well established, providing an elegant explanation for the dual phenotype of PEComas, their mechanistic role in tumorigenesis is still controversial. To date, 3 different models have been proposed to explain the induction of tumor development by *TFE3* translocations.[11] The first model presumes a wild-type tumor-suppressor activity of *TFE3*, which is disrupted by the gene fusion. The second model ascribes a novel transforming activity to the *TFE3* fusion protein because of altered protein conformation. Finally, the third model attributes a more active and less tightly regulated transcriptional activity to the fusion protein, which displays more promiscuous promoter-binding properties than wild-type *TFE3*.[11] Interestingly, some studies have described an increased activation of mTORC1 signaling in *TFE3*-fusion RCC cell lines, suggesting a potential link between the 2 major pathways underlying the molecular pathogenesis of PEComas.

A recurrent translocation involving the *RAD51B* (DNA repair protein RAD51 homolog 2) gene on the long arm of chromosome 14 was also identified in 3 cases.[10] Although only 1 of the 9 neoplasms that showed a *TFE3* translocation originated in the uterus, translocations involving *RAD51* were identified exclusively in uterine PEComas.[10] Interestingly, *TSC2* mutations seemed to be mutually exclusive with *TFE3* translocations, because only *TFE3* translocation–negative PEComas showed *TSC2* mutations and vice versa.[10] Also, 5 of 8 translocation-negative/*TSC2*-mutated PEComas showed synchronous mutations of *TP53* (tumor protein 53).[10] Authors[12] from the University of Pennsylvania demonstrated increased expression of *TP53* by immunohistochemistry in pure epithelioid PEComa, compared with conventional angiomyolipoma. They also documented the presence of *TP53* mutations in some cases of pure epithelioid PEComa, but not in angiomyolipomas.[12] These findings suggest that alterations in the *TP53* pathway may be a possible explanation for the more aggressive biology and unpredictable clinical behavior of pure epithelioid PEComas.

CLINICAL FEATURES

In our literature search, we found 16 reports of clinically aggressive PEComas of the uterine corpus (CAPUs), comprising a total of 20 cases (Table 1).[13–28]

Perivascular epithelioid cell tumors of the uterine corpus can occur in women of any age, including prepubertal pediatric patients.[20] While 5% of all uterine PEComas occur in the context of tuberous sclerosis, most tumors seem to be sporadic.[7] For published CAPUs in particular, there is only one case affecting a patient with tuberous sclerosis, to the best of our knowledge.[14] The mean and median ages at presentation are 47.9 and 44 years, respectively. Most patients have long-standing abdominal pain and vaginal bleeding, but a case with an acute presentation due to uterine rupture has also been documented.[19] Most lesions are initially diagnosed by ultrasonography, usually followed by computed tomography or magnetic resonance imaging to evaluate the anatomic extent of the disease.[14,15,18–20,23,24]

Although intraperitoneal implants are often found at the time of initial diagnosis, distant metastases are most commonly encountered during follow-up.[13,14,18,23] For those cases that show localized disease at presentation, the time to distant metastasis seems to be widely variable, ranging from 1 month to 15 years, with median and mean times to distant metastasis of 90 and 51.2 months, respectively.[16,18,21,22,25–27] Local dissemination in the form of ovarian and pelvic implants is found in 19% (4 of 21) and 14.3% (3 of 21) of CAPUs, respectively. Distant dissemination affects 62% (13 of 21) of patients, and more often involves the lungs (52.4%; 11 of 21), liver (19%; 4 of 21), and bone (14.3%; 3 of 21). Although CAPUs seem to have a preference for hematogenous dissemination, lymph node metastases are also encountered in almost a fifth of cases (4 of 21).[14,17,20,24] Interestingly, 2 patients who developed late metastases, that is, beyond 5 years of initial diagnosis, originally presented with tumors that fell on the lower end of the size spectrum.[16,22] In contrast, most cases with peritoneal and pelvic implants have bulky disease at initial diagnosis.[15,18,23] It is possible that intraperitoneal dissemination occurs as a consequence of microscopic or macroscopic rupture of the serosa overlying the tumor. In this regard, one report describes the development of multiple pelvic implants after spontaneous intraperitoneal rupture of a uterine PEComa.[19] Interestingly, CAPUs that develop intraperitoneal implants or lymph node metastases do not seem to show a tendency for distant dissemination, suggesting that their biology might be different from that of hematogenously metastasizing CAPUs.*

* *References 13–15, 17, 19, 20, 23, 24.*

Table 1. Summary of Clinically Aggressive Perivascular Epithelioid Cell Tumors Reported in the Literature[a]

Authors, y	Age	Disease Extension[b]	Tuberous Sclerosis	Treatment	Follow-up	Outcome
Ruco et al,[13] 1998	56	Ovarian and ileal implants at presentation	No	N/S	N/S	N/S
Bonetti et al,[14] 2001	19	Pelvic and inguinal LN involvement at Dx, lungs and vertebral spine mts during f/u	No	Surg + cht (Adriamycin/ ifosfamide) + consolidation rxt	18 mo	Alive at latest f/u
	41	Right ovarian implants at dx	Yes	Surg	6 mo	Alive/DF at last f/u
Greene et al,[15] 2003	79	Pelvic sidewall and colonic mesentery implants 2 years after initial surgery	N/S	Surg + paclitaxel (1 dose after second, debulking, surgery)	>2 y	DOD at unspecified time during f/u
Dimmler et al,[16] 2003	61	Lung mts 7 y after initial dx	N/S	Surg	7 y	N/S
Daraï et al,[17] 2004	18	Pelvic implants + LN involvement 6 mo after Surg	No	Surg	30 mo	Alive/DF at last f/u
Fukunaga,[18] 2005	40	Omental and ovarian implants at dx, intestinal and lung mts 16 mo after surgery	No	Surg + cht + rxt	17 mo	DOD at 17 mo f/u
Bosincu et al,[19] 2005	59	Free-floating abdominal tumor fragments at dx, pelvic implant 6 mo after surg	No	Surg	6 mo	DOD at 6 mo f/u
Jeon and Lee,[20] 2005	9	LN involvement at dx	No	NeCht (vincristine/ ifosfamide/ doxorubicin) + Surg + rxt	1.5 y	Alive/DF at last f/u
Folpe et al,[21] 2005	59	Liver and lung mts 30 mo after dx	No	Surg + cht	30 mo	Alive with mts at last f/u
	36	Lung mts 2 y after dx, liver mts 3 y after dx	No	Surg + cht	39 mo	DOD at 39 mo f/u
	56	Lung + bone mts 11 mo after dx	No	Surg + cht + rxt	11 mo	Alive with mts at last f/u
Armah et al,[22] 2007	59	Lung and renal mts 7 y after dx	N/S	Surg for the primary tumor and mts	99 mo	Alive/DF at last f/u
Bleeker et al,[23] 2012	50	Ovarian implants at dx	No	Surg	18 mo	Alive/DF at last f/u
Liu et al,[24] 2009	33	LN involvement at dx	No	NeCht + surg + cht (epirubicin + cisplatin + ifosfamide)	8 mo	Alive/DF at last f/u
Yamashita and Fletcher,[25] 2010	42	Bone mts 1 y after dx	N/S	Surg + cht	22 mo	DOD at 22 mo f/u
Cossu et al,[26] 2014	52	Lung and liver mts 3 y after dx	N/S	Surg	60 mo	DOD at 60 mo f/u
Kang et al,[27] 2014	49	Lung mts at 7 mo	N/S	Surg + cht (doxorubicin hydrochloride + haloxan)	7 mo	Alive at last f/u
Italiano et al,[28] 2010	69	Lung metastasis at initial dx	N/S	Surg + mTOR inhibitor + metastasectomy	9 mo	Alive/DF at last f/u
	55	Cardiac and thoracic mts 15 y after initial dx, liver mts 16 y after initial dx	N/S	Sug + metastasectomy (for cardiac and thoracic mts) + cht (Adriamycin/ ifosfamide and gentamycin) and mTOR inhibitor (for the liver mts)	16.7 mo	Alive with mts and disease progression at last f/u

Abbreviations: cht, adjuvant chemotherapy and/or chemotherapy for the treatment of metastatic disease; DF, disease-free; DOD, died of disease; Dx, diagnosis; f/u, follow-up; LN, lymph node; mTOR, mammalian target of rapamycin; mts, metastasis; NeCht, neoadjuvant chemotherapy; N/S, not specified; rxt, radiotherapy; Surg, surgery.

[a] Perivascular epithelioid cell tumors that showed evidence of regional or distant dissemination, requiring surgery or chemotherapy at the time of initial presentation or during follow-up.

[b] Other than direct local extension.

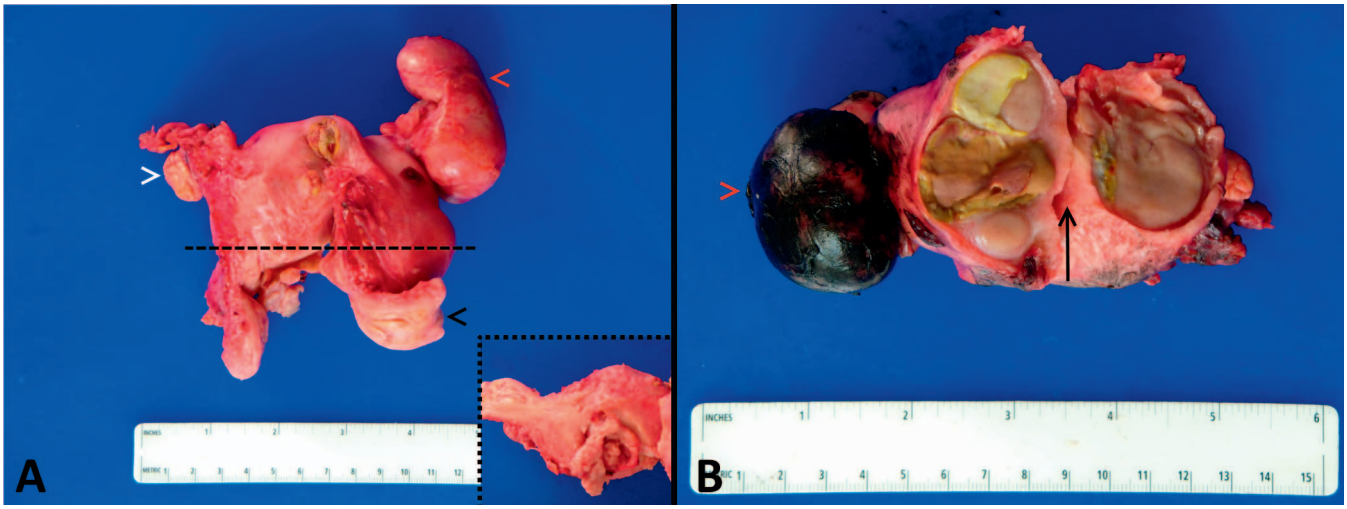

Figure 1. *Clinically aggressive perivascular epithelioid cell tumor of the uterine corpus, macroscopy. A, Right lateral view of a bisected uterus. The uterine corpus is distorted by multiple myometrial nodules and a large subserosal nodule (red arrowhead). A black arrowhead indicates the cervix, and a white arrowhead indicates the right ovary. The dashed line indicates the section plane of the specimen shown in B. The bivalved uterus shows a prominent polypoid intracavitary tumor (inset). B, A horizontal section plane above the cervix reveals a greatly distorted endometrial cavity (black arrow). The tumor shows a multinodular structure with a gray to tan smooth cut surface with grossly evident necrosis. The subserosal tumor is inked black (red arrowhead).*

PATHOLOGIC FEATURES AND DIFFERENTIAL DIAGNOSIS

Macroscopically, most CAPUs are described as nodular or multinodular lesions with a myometrial or subserosal localization and a fungating appearance.[13–20,22–24] Also, nodules with a submucosal localization can present clinically as pedunculated or sessile polyps (Figure 1, A). Most tumors are bulky, ranging from 5 to 30 cm in greatest dimension, with mean and median sizes of 11 and 12.5 cm, respectively (Table 2). The cut surface is pink to gray and homogeneous, but areas of macroscopic necrosis and hemorrhage are also frequently present (Figure 1, B).[6,13–20,22–24]

Perivascular epithelioid cell tumors of the uterine corpus are highly vascular and demonstrate an epithelioid, spindle cell, or combined epithelioid–spindle cell cytomorphology (Figure 2, A).[13–28] Microscopically, most neoplasms show infiltration of the myometrium, with malignant cells splitting the myometrial fibers or infiltrative tonguelike lesional borders.[6,13–27]

The epithelioid cells are medium-sized to large, and show a trabecular, nested, and/or solid arrangement, with a characteristic tendency to aggregate around blood vessels. However, less common papillary and pseudoglandular histoarchitectural patterns have also been described.[14] Individual cells show well-defined borders and an abundant, granular, eosinophilic to clear cytoplasm that can display diastase-sensitive periodic acid–Schiff positivity.[20] Nuclear pleomorphism is usually moderate to marked, but rare cases can show uniform nuclei with bland cytomorphologic features.[16] Large nucleoli and atypical hyperchromatic nuclei with coarsely clumped chromatin are commonly found. In contrast, the spindle cell component of CAPUs is characteristically less atypical, and consists of short fascicles and nests of slender fusiform cells in a stromal background with diverse histologic changes, such as myxoid degeneration (Figure 2, B). Both tumor necrosis and lymphovascular invasion are frequently identified, and their presence in an otherwise typical PEComa should always suggest the possibility of CAPU.[14,15,19,22,24,27] Bizarre mononucleated and multinucleated giant cells are often recognized scattered among the rest of the neoplastic elements.[19,22,24] Also, microscopically apparent intracellular pigment can occasionally be detected in the tumor cells.[14] Mitotic activity is usually high, but not invariably so, with some PEComas showing an aggressive clinical behavior in spite of a low mitotic count.[16,20,24] However, the presence of even a small number of mitotic figures is worrisome, because nonaggressive PEComas show very rare, if any, mitoses.[6] Similarly, the identification of even a single isolated atypical mitotic figure is highly indicative of malignancy. Metastases show histopathologic features similar to those of the primary tumor, with marked nuclear pleomorphism, tumor necrosis, and very high mitotic rates being common findings.[22,25,27]

Electron microscopy reveals multiple granules that resemble promelanosomes, within a cytoplasm that displays ultrastructural features similar to those of smooth muscle cells.[13]

Immunohistochemically, PEComas are characterized by the coexpression of smooth muscle and melanocytic markers (Figure 3, A and B). Among the smooth muscle cell markers, smooth muscle actin, muscle-specific actin, and desmin are positive in 84.6%, 66.7%, and 55.6% of cases, respectively.[13–16,18–20,22–27] The melanocytic marker HMB-45 is expressed in all cases, and Melan-A is positive in up to 80% of tumors.[13–16,18–20,22–27] One case also demonstrated focal nuclear labeling for MiTF, a relatively new melanocyte immunomarker. Although a significant proportion of CAPUs show positivity for estrogen receptor, protein S-100 and cytokeratins are invariably negative.[†]

The World Health Organization[6] classification of tumors of female reproductive organs (2014) proposes the use of 7 parameters to identify those PEComas with a potentially aggressive clinical behavior. Namely, those parameters are

[†] *References 13–15, 19, 20, 22, 23, 25, 26.*

Table 2. Pathologic and Immunohistochemical Features of Clinically Aggressive Perivascular Epithelioid Cell Tumors of the Uterine Corpus

	No.[a]	Mean (Range)
No. of cases	**21**	
Size	**13**	11 cm (5–30 cm)
Location	**8**	
Myometrial	3	
Subserosal	3	
Myometrial/subserosal	2	
Gross hemorrhage	**6**	
Gross necrosis	**8**	
Histology	**19**	
Epithelioid	14	
Epithelioid + spindled	5	
Microscopic necrosis present	**13**	
Microscopic LVI	**12**	
Present	10	
Absent	2	
Pleomorphism	**12**	
Present	11	
Absent	1	
Mitotic rate	**12**	NA (2–50/50 hpf)[b]
Immunohistochemistry, No. positive cases/total No. cases reported (%)		
HMB-45	15/15 (100)	
Melan-A	8/10 (80)	
S100	0/9 (0)	
SMA	11/13 (84.6)	
MSA	4/6 (66.7)	
Desmin	5/9 (55.6)	
ER	3/7 (42.9)	
MITF	1/1 (100)	

Abbreviations: ER, estrogen receptor; HMB-45, human melanoma black 45; hpf, high-power field; LVI, lymphovascular invasion; Melan-A, protein Melan-A; MITF, microphthalmia transcription factor; MSA, muscle-specific actin; S100, protein S100; SMA, smooth muscle actin.

[a] The numbers in bold font indicate the number of cases for which a particular set of data is reported.

[b] Median and mean values could not be calculated because of the absence of uniformity in the denominator of the mitotic counts. Although the World Health Organization classification of tumors of the female reproductive system uses the number of mitotic figures per 50 hpf as a criterion for malignancy, many reports inform the number of mitotic figures per 10 hpf.

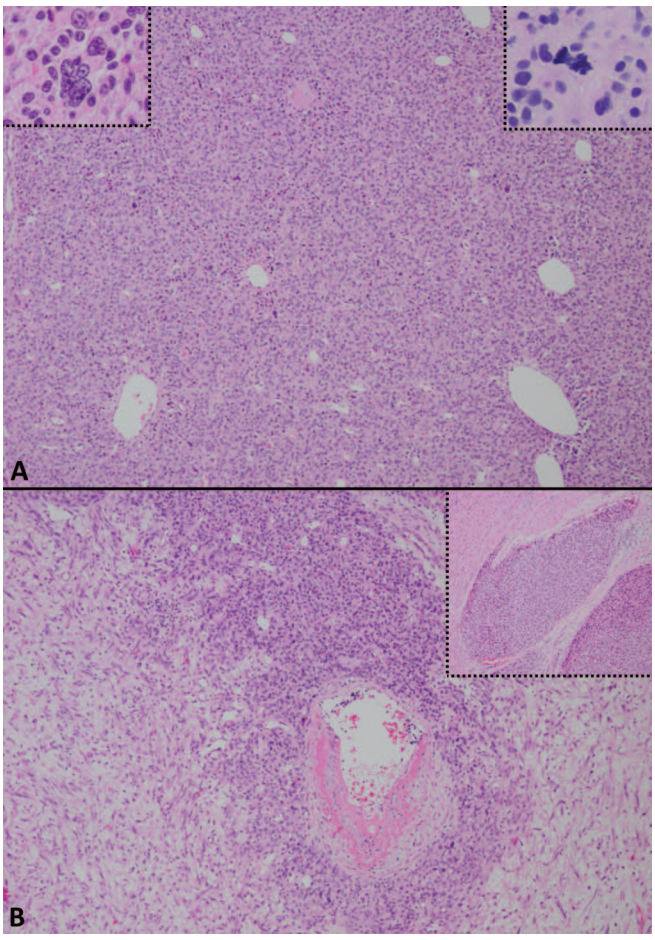

Figure 2. *Clinically aggressive perivascular epithelioid cell tumor of the uterine corpus, histopathology. A, The tumor shows sheets and islands of epithelioid tumor cells, a rich network of prominent blood vessels, and marked nuclear pleomorphism. Scattered giant cells are found throughout the lesion (left inset). Atypical mitotic figures are also identified (right inset). B, A different area of the tumor shows both epithelioid and spindle cells. The former show a perivascular distribution, whereas the latter are situated away from the blood vessels, within a myxoid stroma. Lymphovascular invasion is readily identified at the periphery of the tumor (inset) (hematoxylin–eosin, original magnifications ×100 [A and B], ×400 [A insets] and ×200 [B inset]).*

size larger than 5 cm, infiltrative margins, high-grade nuclear atypia, high cellularity, mitotic activity greater than 1/50 high-power fields, necrosis, and vascular invasion. Although tumors that show either a size larger than 5 cm or nuclear pleomorphism alone might be considered of uncertain clinical behavior, the presence of 2 or more of the aforementioned histopathologic features portends a high risk for aggressiveness.

The differential diagnosis includes leiomyosarcoma (LMS), low-grade endometrial stromal sarcoma (ESS), and high-grade ESS, all of which are more frequent than CAPUs. In this regard, some uterine tumors originally diagnosed as uterine LMS or ESS are retrospectively found to be CAPUs when they are reviewed in the context of an apparently extrauterine PEComa presenting several years later.[22,25] Although all of the aforementioned neoplasms can be positive for sex hormone receptors, an intense estrogen receptor immunolabeling is more often found in low-grade ESS.[6] High-grade ESS, which is usually negative for hormone receptors, can be differentiated from CAPUs by its diffuse cyclin D1 positivity, especially if melanocytic immunomarkers are negative.[6] In addition, the demonstration of a (10;17) translocation, which results in the YWAEH-FAMM22 (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon family with sequence similarity 22) fusion product, strongly favors the diagnosis of high-grade ESS. Likewise, the presence of a rearrangement of PHD finger protein 1 (PHF1) gene on chromosome 6, or a translocation (7;17)(p15;q21) is highly suggestive of low-grade ESS.[6]

Coexpression of smooth muscle markers and discovered on gastrointestinal stromal tumor 1 (DOG1), together with a negative immunolabeling for melanocytic antigens, favors a diagnosis of LMS.[6] An important pitfall to be aware of is that ESS, LMS, and even leiomyomas can all occasionally show expression of HMB-45.[29,30] As a matter of fact, as many as 25% of LMSs and 23.5% of ESSs can be HMB-45 positive.[29,30] In LMS, positivity for HMB-45 is more often

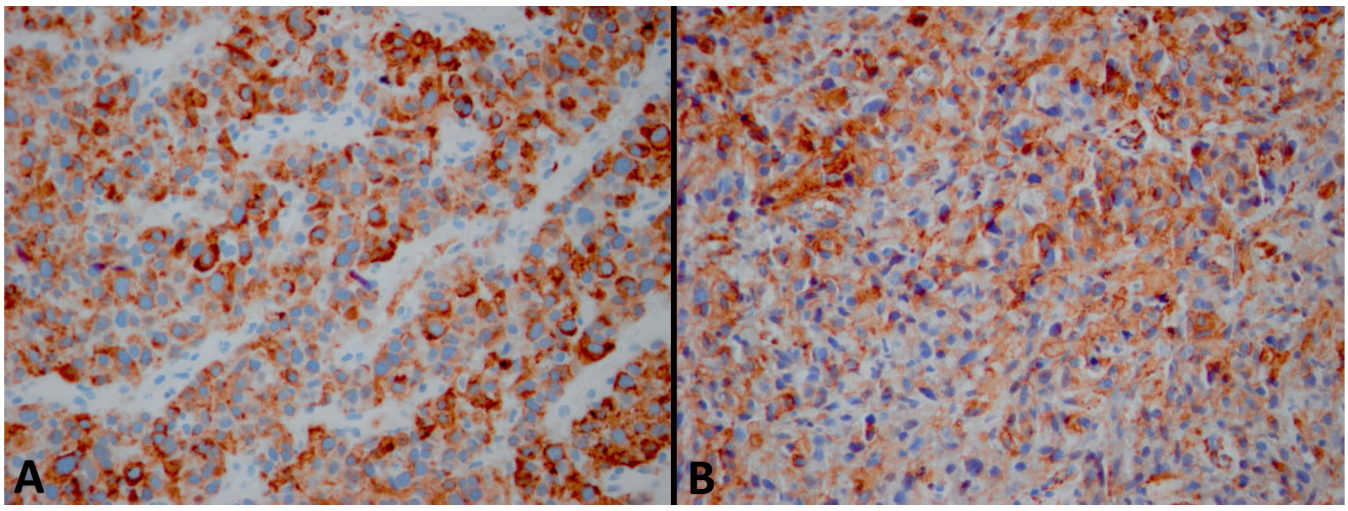

Figure 3. *Clinically aggressive perivascular epithelioid cell tumor of the uterine corpus, immunohistochemistry. The tumor cells are positive for Melan-A (A) and smooth muscle actin (B) (original magnification ×100).*

found in high-grade tumors.[29] Although this can be problematic, because such an immunoprofile would be indistinguishable from that of a PEComa, HMB-45 expression in LMS is usually present focally in a minor subset of tumor cells.[29] In contrast, PEComas tend to show a more diffuse and intense positivity for melanocytic markers. In difficult cases, immunolabeling for more than one melanocytic marker, as well as the demonstration of TSC2 mutations or TFE3 translocations, might be helpful to differentiate PEComa from LMS. The presence of melanocytic antigens in ESS is probably less problematic, because these tumors show additional immunomarkers that are not usually found in PEComas, and they also harbor specific chromosomal rearrangements.

The diagnosis of metastatic PEComa can often prove to be problematic, because both pelvic lymph nodes and lungs can be affected by lymphangioleiomyomatosis. In this review, we only included cases where lymph node and pulmonary involvement was deemed metastatic by the authors and therefore treated accordingly. For pulmonary metastases, correlation with the clinical course and radiologic findings are elements that can be used to determine their secondary nature. Specifically, the development of new lesions during follow-up that have a solid, nodular appearance on computed tomography—instead of the characteristically cystic look of lymphangioleiomyomatosis—and show an aggressive clinical behavior strongly favors the diagnosis of metastatic PEComa.[16,18,27] Also, the presence of overtly malignant features, such as mitoses and necrosis, is highly indicative of tumor implants, especially when those same features were present in the primary tumor.[22] For lymph node metastases and abdominopelvic implants, 2 important factors that suggest their secondary nature are the identification of distinctly malignant histologic features and an aggressive, infiltrative growth.[14,18,19]

TREATMENT AND PROGNOSIS

Surgery, either with a cytoreductive or curative intent, is the mainstay of therapy for CAPUs.[13–28] Most patients who show distant metastases or lymph node involvement receive adjuvant treatment in the form of chemotherapy or chemoradiation.[14,18,20,21,24,25] However, one patient with lung and kidney metastases who refused adjuvant treatment has been reported to be disease free 1.5 years after a combined metastasectomy.[22] Also, 2 patients with ovarian implants and no evidence of lymph node or distant metastases have been treated with surgery alone, remaining recurrence free at 6 and 18 months of follow-up, respectively.[14,23] Neoadjuvant chemotherapy has been used in 2 patients who presented initially with bulky local disease, allowing for a subsequent radical surgery.[20,24] The use of mammalian target of rapamycin (*mTOR*) inhibitors for the treatment of CAPUs relies on the rationale that these tumors often harbor *TSC2* mutations. Studies on small groups of patients with CAPUs from different anatomic locations have reported a good clinical response to *mTOR* inhibitors.[28,31,32] In fact, individual cases with bulky, unresectable disease at presentation have shown complete or near-complete sustained clinical responses to these drugs.[32] Moreover, *mTOR* inhibitor therapy followed by surgical resection of a single metastasis has proven to be beneficial in at least 2 patients, who have remained disease free at 6 and 9 months after metastasectomy, respectively.[28,32] It must be noted, however, that there are several cases where clinical response is either absent or minimal and short-lived because of the development of resistance against mTOR inhibitors. This suggests that, when selective pressure is applied, alternative molecular mechanisms may eventually override the mTOR-driven tumorigenesis.

With regard to prognosis, some cases show an aggressive local disease with early dissemination, whereas others display a more indolent course characterized by late distant metastases. Patients with bulky pelvic disease seem to fare poorly, often exhibiting little response to adjuvant treatment and early disease-related mortality.[15,18,19] In contrast, those patients who develop late metastases—several years after the initial diagnosis—appear to have a more protracted clinical course and better overall survival, despite the presence of disseminated disease.[21,22,27,28]

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