Soft Tissue Perivascular Epithelioid Cell Tumors

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Key points

- PEComa family of tumors arising in soft tissue is rare and includes PEComas (not otherwise specified) and extrarenal angiomyolipomas.
- Most soft tissue PEComas are sporadic, with a small subset associated with tuberous sclerosis complex.
- PEComas are characterized by epithelioid and/or spindled cells with distinct perivascular orientation and variable myomelanocytic immunophenotype.
- Histologic criteria for malignancy include tumor size greater than 5 cm, increased mitoses, necrosis, infiltrative growth pattern, high nuclear grade, cellularity, and vascular invasion.
- PEComas show either *TSC1/2* loss or *TFE3*-rearrangements; molecular testing can be helpful diagnostically and therapeutically.

ABSTRACT

Perivascular epithelioid cell tumors (PEComas) are a heterogenous group of mesenchymal neoplasms with a mixed myomelanocytic immunophenotype. PEComa-family tumors include angiomyolipoma, lymphangioleiomyomatosis, and a large category of rare neoplasms throughout the body that are now classified under the umbrella term "PEComa." This review focuses on recent advances in the clinicopathological and molecular features of PEComas, with an emphasis on PEComas that originate in soft tissue.

OVERVIEW

Perivascular epithelioid cell tumors (PEComas) are a heterogenous family of mesenchymal neoplasms composed of morphologically distinct perivascular epithelioid cells (PECs) that usually express both melanocytic and smooth muscle markers.[1] In a correspondence published in 1991, Bonetti and colleagues[2] first proposed a link between HMB-45 immunoreactive clear cell "sugar" tumor (CCST) of the lung, the epithelioid component of angiomyolipomas (AMLs), and pulmonary lymphangioleiomyomatosis (LAM) and subsequently proposed the term "perivascular epithelioid cell" to describe the morphologically and immunohistochemically distinct cell found in these neoplasms.[3] They hypothesized that PECs might originate from the walls of blood vessels.[3] Zamboni and colleagues[4], in a report of pancreatic CCST, suggested the term *PEComa* to describe a neoplasm composed entirely of PECs. The PEComa family has since expanded to include rare visceral, intra-abdominal, soft tissue, bone, and cutaneous tumors described variously in the past as "primary

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extrapulmonary sugar tumor,"[5] "abdominopelvic sarcoma of perivascular epithelioid cells,"[6] "clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres,"[7] and "cutaneous clear cell myomelanocytic tumor,"[8] among others, and which are now broadly known as PEComas not otherwise specified or simply PEComas.[1] In the current WHO classification of soft tissue tumors, PEComas are subdivided into benign, intermediate, and malignant subgroups,[9] and related tumors include AML, epithelioid AML, and LAM.

This review describes the PEComa family tumors that arise in soft tissues, including PEComa, extrarenal AML, and extrarenal epithelioid AML (synonymous with PEComa).

CLINICAL FEATURES

PEComas have been reported in nearly all anatomic sites but are most frequently found in the genitourinary[10] and gynecologic tract,[11,12] followed by the gastrointestinal tract[13] and retroperitoneum,[14] and are rarely in somatic soft tissue, bone, and cutaneous sites.[1,8,15] A large variety of soft tissue sites have been described, including retroperitoneum, omentum and mesentery, abdominal wall, pelvic soft tissues, and deep and superficial soft tissue of the extremities and trunk.[1] There is an overall female predominance (approximately 5:1).[9]

Most PEComas show alterations in *TSC1* or *TSC2* including select subtypes, most notably renal AML and LAM, which show strong association with tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder caused by germline mutations in either *TSC1* on chromosome 9 or *TSC2* on chromosome 16.[16] Among soft tissue PEComas, fibroma-like PEComas are highly associated with this syndrome.[17] Although most soft tissue PEComas are not associated with TSC,[1] many show alterations in *TSC2*. *TFE3* rearrangements represent an alternative molecular pathway of tumorigenesis. With rare exception,[18] *TFE3*-rearranged PEComas are not seen in patients with TSC,[19] tend to occur in young patients, and are usually seen in the gynecologic, genitourinary, and gastrointestinal tracts in addition to soft tissue sites.[13,20–22]

PATHOLOGIC FEATURES

PEComas are composed of epithelioid, spindled, and lipid-rich cells. Great variation is seen in the relative components,[23] with gross and

Fig. 1. Epithelioid PEComas. A vascular component is usually prominent and may include arteries/arterioles with hyalinized walls (*A*), hemangiopericytoma-like vessels (*B*), or delicate capillaries (*C*).
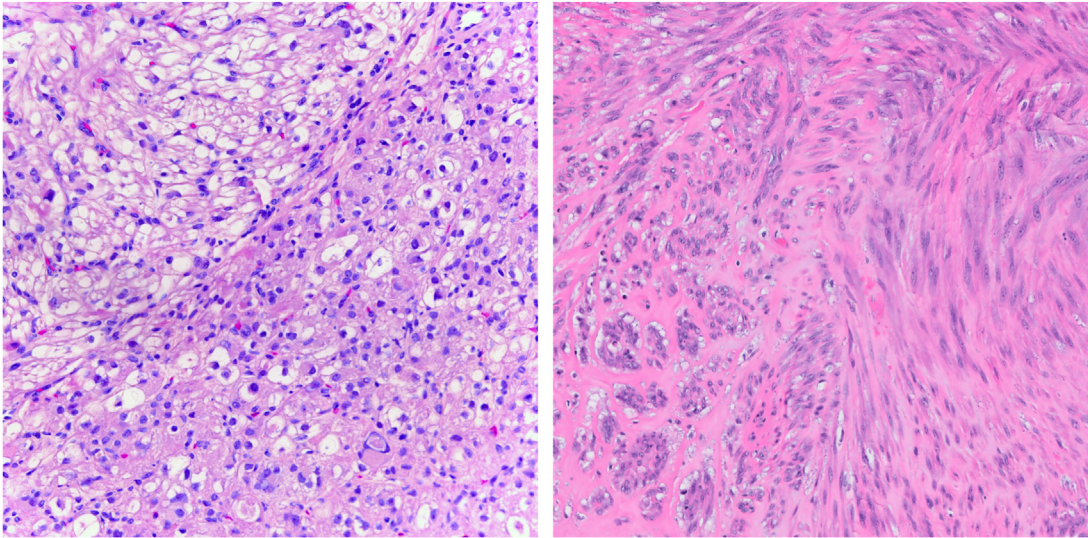
Fig. 2. PEComas with mixed epithelioid and spindled morphology.

microscopic features differing depending on predominant histomorphology. They are unencapsulated, may be well circumscribed or infiltrative,[1,13] and demonstrate a large size range. Microscopically, most soft tissue PEComas are lipid poor and demonstrate a mix of epithelioid and spindled cells, although predominant or pure epithelioid or spindled varieties exist. A lipomatous component is more prominent in classic AMLs, which tend to occur in the kidney but are found rarely in the soft tissue ("extrarenal AMLs"). *TFE3*-rearranged PEComas often demonstrate distinctive morphologic and immunophenotypic features; other variations include sclerosing and fibroma-like PEComas and PECosis/ PEComatosis.

Many soft tissue PEComas have predominantly or purely epithelioid cells and are morphologically indistinguishable from renal epithelioid AMLs. In current practice, extrarenal epithelioid AMLs are referred to as "PEComas," even though the renal tumors continue to be referred to as epithelioid AMLs. The epithelioid cells are characteristically large and polygonal with clear to granular, eosinophilic cytoplasm, growing in sheet-like or nested arrangements,[1,13,14] and may be closely
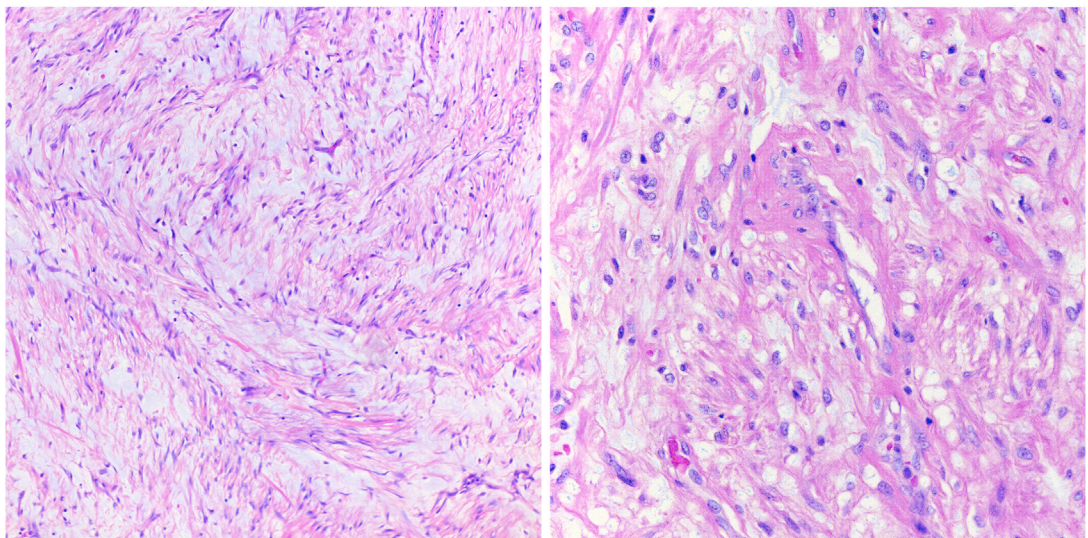

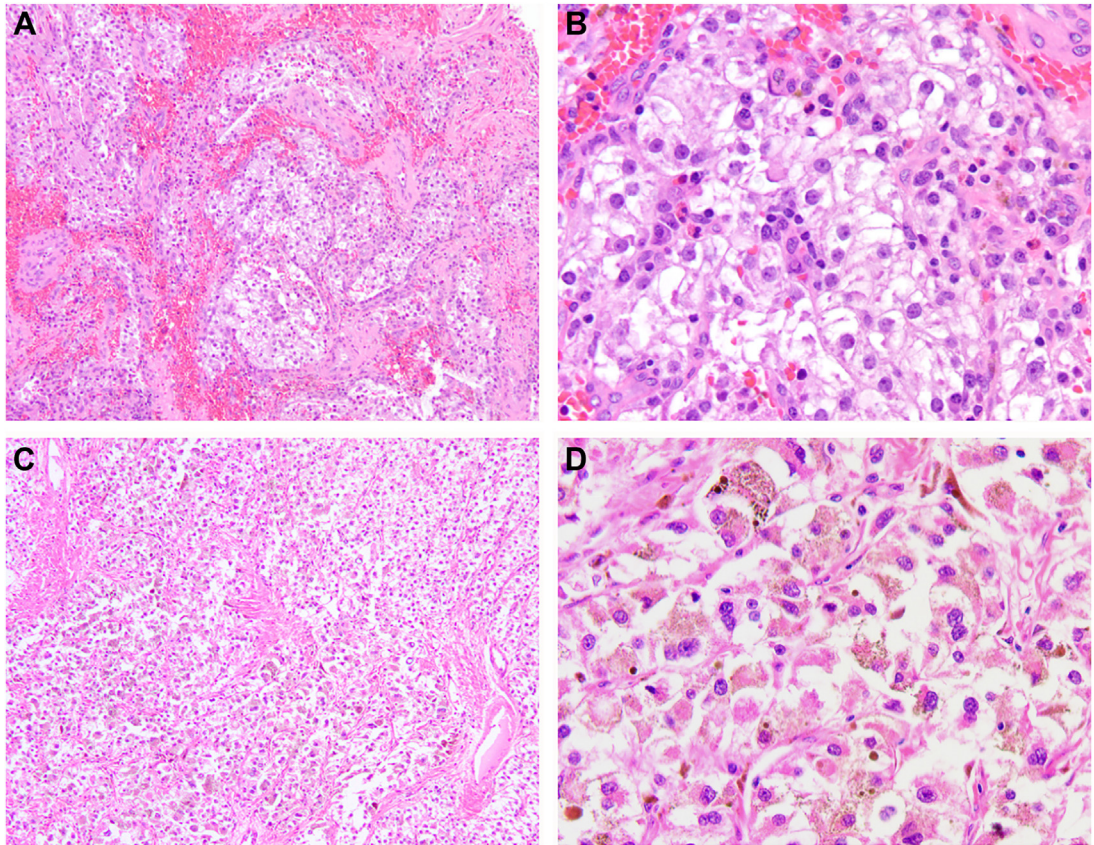*Fig. 3.* PEComas with predominantly spindled morphology.

Fig. 4. Examples of *TFE3*-rearranged PEComas with nested and alveolar architecture. Tumors may have associated hemorrhage and inflammatory cells (*A, B*) and sometimes contain melanin pigment (*C, D*). (Photomicrographs courtesy of Andrew L Folpe, M.D., Rochester, Minnesota.).

associated with vessel walls, at times with a distinctive radial arrangement around the vascular lumens.[14,23] Their nuclei are round to ovoid with variably small nucleoli, although some tumors may show striking cytologic atypia with large, prominent nucleoli. A population of plump spindle cells may be present. There is nearly always a prominent vascular component, ranging from delicate, arborizing capillaries to thick hyalinized arterioles or arteries (**Fig. 1**).[1] Multinucleated giant cells, intranuclear pseudoinclusions, and melanin pigment are occasionally observed.[1,12,23]

Spindle cells in PEComas are typically myoid-appearing, with eosinophilic to clear cytoplasm and arranged in fascicles.[13] Although they usually accompany an epithelioid component (**Fig. 2**), pure or predominant spindle morphology has been described in a minority of PEComas[1,13] (**Fig. 3**), initially in a group of tumors called "clear cell myomelanocytic tumor" (CCMT), noted first in the falciform ligament/ligamentum teres and

subsequently in somatic soft tissue.[24] Since then, more examples of PEComas with pure spindle morphology have been reported.[1,13] We now recognize that CCMT is a morphologic variant of PEComas and not a distinct entity; hence, the use of this term is discouraged.[9]

TFE3-rearranged PEComas are usually epithelioid predominant and are characterized by nested or alveolar arrangement with associated delicate, thin-walled vasculature,[20] along with a variable spindle cell component[22,25] and collagenized stroma.[20] The epithelioid cells contain clear cytoplasm and demonstrate a range of atypia (**Fig. 4**).[22] Occasionally, they are morphologically indistinguishable from conventional PEComas.[25]

Sclerosing PEComas represent a subtype of PEComa that shows prominent stromal hyalinization (**Fig. 5**). They represent approximately 20% of PEComas, have a predilection for adult women and the retroperitoneum,[26] but have also been identified in the testis[27] and kidney,[28] rarely in
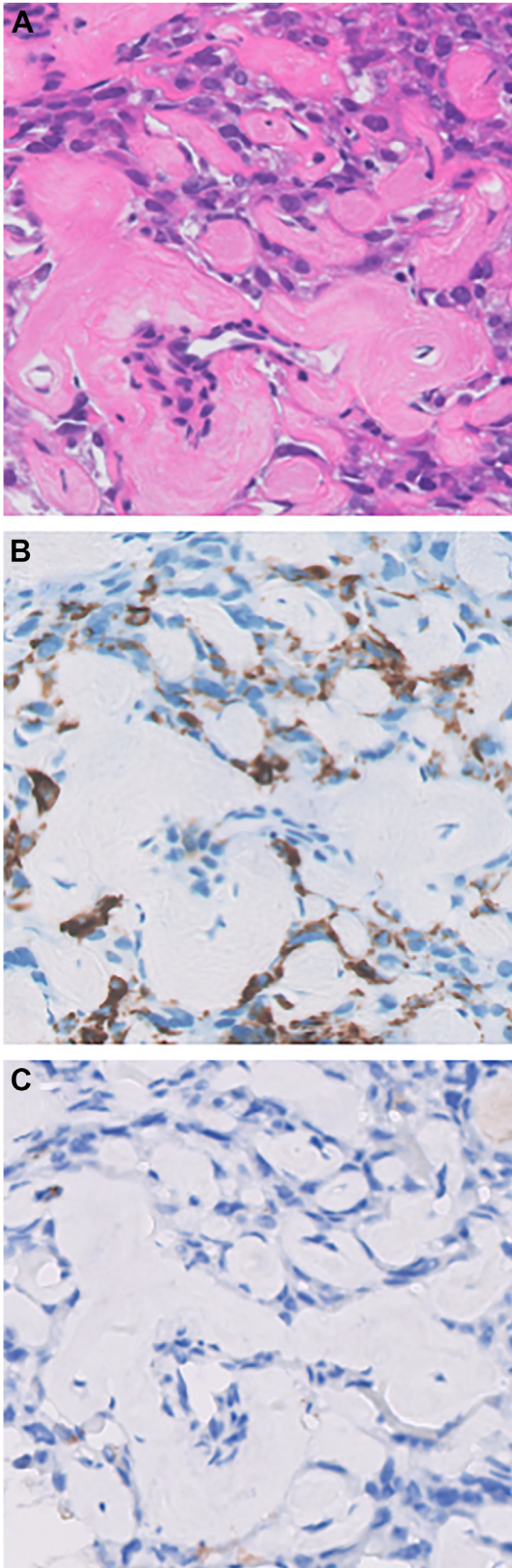
the TSC context.[26,27] Morphologically, epithelioid cells are embedded in an abundant densely sclerotic stroma and lack the delicate vascular pattern typical of other PEComas.[26] Immunophenotypically, they show more muscle and less melanocytic marker expression than most PEComas (details in *Immunohistochemical Features*). In the absence of a frankly malignant component, sclerosing PEComas appear to behave in an indolent manner.[26]

Fibroma-like PEComa is a recently described subtype of PEComa that arises in association with TSC and resembles a fibroma by conventional morphology.[17] Fewer than 10 cases have been reported in the literature, most of which have been in younger patients and in soft tissue locations.[17,29–32] Grossly, tumors appear well-circumscribed, solid, and rubbery. Morphologically, they are characterized by bland spindled to stellate cells with no obvious organization embedded in abundant collagenous stroma. No cases have shown abnormalities in *TFE3*. All tested cases showed expression of at least one melanocytic and one muscle marker.[17,29–32] Given its apparent association with TSC, the identification of these morphologic features should raise consideration for germline testing if TSC is not already established.

While rare, extrarenal AMLs have been described in soft tissue sites, most commonly in the retroperitoneum.[33] In contrast to most other soft tissue PEComas, which are lipid poor and commonly epithelioid predominant, classic AMLs are characterized by "classic triphasic pattern" comprising a variable mix of mature adipose tissue, disorganized thick-walled blood vessels and spindled to epithelioid myoid cells (**Fig. 6**).[14] Owing to their atypical location, they present a unique diagnostic challenge.

PEComatosis/PECosis

PEComas usually appear as solitary tumors; however, rare reports of multifocal PEComas and/or microscopic proliferations of PECs have been described. The presence of multiple proliferations of PECs in a perivascular distribution has been termed "PEComatosis."[34] Less frequently, the term "PECosis" has been used to describe the phenomenon of multifocal PECs with distant dissemination through the capillary network,[35] leading to degeneration of surrounding tissue. PEComatosis has largely been described in the gynecologic tract and visceral locations, although it stands to reason that this phenomenon may occur in other anatomic sites.
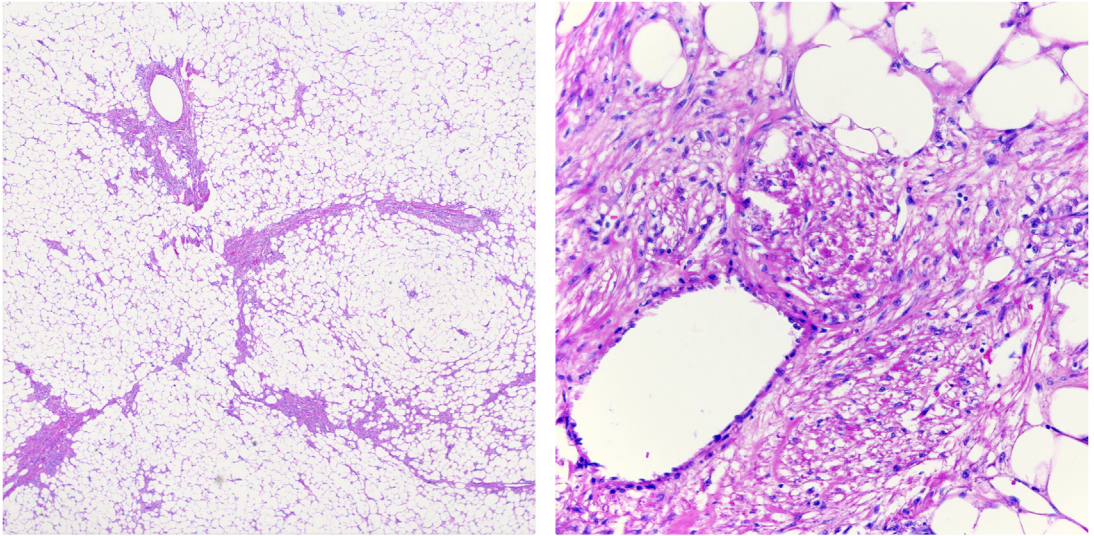
Fig. 5. Sclerosing PEComa (*A*) with stronger expression of desmin (*B*) than HMB45 (*C*).

Fig. 6. Retroperitoneal AML composed predominantly of adipose tissue with interspersed vessels and a smaller smooth muscle component.

IMMUNOHISTOCHEMICAL FEATURES

PEComas are uniquely characterized by the expression of melanocytic and muscle markers, which show variable sensitivity (**Table 1**). HMB45 and cathepsin K are the most sensitive markers for PEComa in multiple anatomic sites.[1,12,36] Besides HMB45, other useful melanocytic markers include microphthalmia transcription factor (MiTF)[1,37] and MART-1/Melan-A.[1,11] More recently, PNL2 has shown moderate to high sensitivity[38,39] and may show more diffuse staining than HMB45.[38] Muscle markers are usually weaker, with focal or patchy expression.[1] Smooth muscle actin (SMA) is the most sensitive reported muscle marker[1,11,19,39–42]; desmin and caldesmon have shown a widely ranging sensitivity in studies on uterine PEComas.[1,19,39–41] Cytokeratin stains are negative.[1] S100 protein is generally negative, but may be at least weakly or focally positive in ~10% to 30% of tumors.[1,13] Although single-specific immunohistochemical stains for PEComas are lacking, the dual expression of at least one melanocytic marker and one muscle marker provides strong support for PEComa.

Variable relative expression of melanocytic and muscle markers has been observed in different subsets of PEComas, depending in part on their relative epithelioid and spindle components.[23] The epithelioid-appearing cells tend to express melanocytic markers more strongly than muscle markers, and myoid-appearing cells tend to show the opposite.[23] This variation has been described in greatest detail in the context of distinguishing uterine PEComas from smooth muscle and other mesenchymal lesions that can demonstrate myomelanocytic differentiation.[43,44] Sclerosing PEComas are reported to show the extensive expression of desmin, in contrast to other types of PEComas; although only patchy HMB45 is present, nuclear staining for MiTF is identified in most tumors and is usually extensive.[26] PEComas with *TFE3* rearrangement notably show weak or no expression of smooth muscle markers,[20,22] in addition to strong expression of HMB45 and cathepsin K, and variable expression of Melan-A.[20,22] *TFE3*-rearranged PEComas demonstrate strong expression of TFE3 by IHC, although a subset of *TFE3* fluorescence in situ hybridization (FISH)-negative tumors also show weak to moderate expression of TFE3.[20]

MOLECULAR FEATURES

Two major and distinct biological pathways of tumorigenesis in PEComa family tumors have been described—loss of function of *TSC1* or *TSC2* mutations and alternatively, *TFE3* gene rearrangements.[19] The loss of heterozygosity (LOH) of *TSC1* or *TSC2* is detected in PEComas arising in patients with TSC.[23,45] Outside of the TSC context, molecular studies in sporadic AMLs,[46,47] LAM,[48,49] and PEComas[19,50] have also demonstrated LOH in *TSC2*; *TSC1* LOH is only rarely detected in sporadic PEComas.[50] Pathogenic inactivating mutations of *TSC1/TSC2* lead to upregulation of the mammalian target of rapamycin (mTOR) pathway in PEComa family tumors that

Table 1
Immunohistochemical features of perivascular epithelioid cell tumors

Positive	Negative
Cathepsin K (100%)[1,13,30]	Cytokeratins (rare focal positivity)[1]
HMB45 (>90%)[1,13,30]	PAX8
MiTF (50–66%)[1,31]	S100 (focally positive in 10–30%)[1,14]
MART-1/Melan-A (46–72%)[1,31]	SOX1011
PNL2 (56%-85%)[32,33]	PRAME77
Smooth muscle actin (75–93%)[1,12,29,33–36]	CD34
Desmin (36–100%)[1,33–36]	DOG1
Caldesmon (64–92%)[1,33–36]	CD117 (focally positive in 30% of PEComas)[1]
Unique immunohistochemistry (IHC) Considerations	
Epithelioid predominant	Express melanocytic markers more strongly than myogenic markers
Spindled predominant	Express myogenic markers more strongly than melanocytic markers
TFE3-rearranged	Nuclear staining for TFE3[a], strong expression of melanocytic markers, weak or no expression of myogenic markers
Sclerosing subtype	Express myogenic markers (notably desmin) more extensively than melanocytic markers

[a] Note that TFE3 IHC is nonspecific and can be positive in tumors that lack TFE rearrangements.

can be targeted therapeutically with mTOR inhibitors.[51]

The second molecularly distinct subgroup of PEComas harbor *TFE3* abnormalities[20] and involve approximately 20% of non-AML, non-LAM PEComas.[19] *TFE3*-rearranged PEComas demonstrate unique clinical and histopathologic characteristics that have already been described.

They lack the *TSC2* LOH seen in the majority of PEComas, providing support for a biologically distinct pathogenesis,[52] and are important to recognize due in part to their differential response to mTOR inhibition. FISH for *TFE3* rearrangements or detection of a *TFE3* fusion via next-generation sequencing (NGS) can establish the molecular features. The lack of specificity of TFE3 IHC precludes diagnosis based on IHC alone, and molecular testing is needed to confirm *TFE3* abnormalities.

Concurrent mutations in *TP53* have also been identified in *TSC*-altered PEComas.[19,43,44] In malignant PEComas, up to 48% to 63% of tumors demonstrate *TP53* abnormalities.[19,44,53] In addition, rare cases of both clinically benign and malignant PEComas in young adult patients with Li-Fraumeni syndrome (LFS) have been reported,[54,55] including concurrent diagnosis of PEComas in siblings with LFS.[54] The possible relationship between LFS and PEComas raises an important clinical consideration when diagnosing young patients with PEComa.

ASSESSMENT OF MALIGNANCY AND PROGNOSIS

PEComas show a range of clinical behavior, from benign to highly aggressive. Diagnostic criteria for aggressive behavior and malignancy continue to evolve.

The prognostic classification system established by Folpe and colleagues[1] divides PEComas into benign, uncertain malignant potential (UMP), and malignant based on six criteria: tumor size $\geq$ 5 cm, mitotic rate greater than 1/50 high-power fields, necrosis, an infiltrative growth pattern, high nuclear grade, and vascular invasion. Tumors lacking any of these features are considered benign, whereas tumors with at least two of these features are considered malignant (**Figs. 7** and **8**). The UMP category is applied to tumors with only a single histological feature, such as nuclear pleomorphism or multinucleated giant cells, or size $\geq$ 5 cm without other aggressive features.[1] These criteria have been substantiated for non-gynecologic sites.[56]

Molecular prognostic approaches for subsets of PEComas are starting to emerge. The prognostic understanding of *TFE3*-rearranged PEComas is incomplete, although cases with an aggressive clinical course and metastases have been reported. Multiple cases of malignant *TFE3*-rearranged or amplified PEComas have been recently reported,[18,21,57,58] with amplifications demonstrating a highly aggressive clinical course.
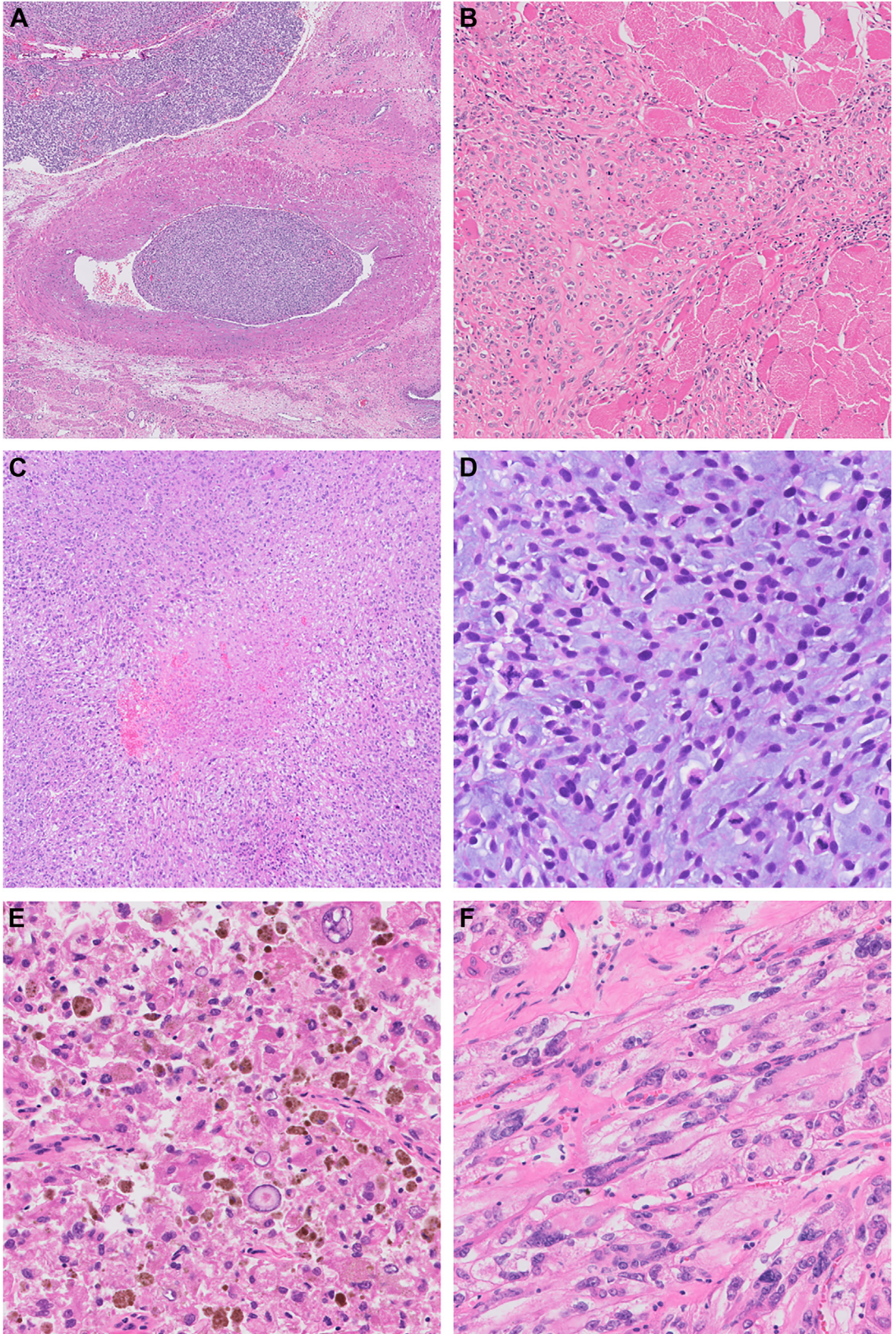
Fig. 7. Features of malignant PEComas. Malignant tumors may demonstrate vascular invasion (*A*), infiltration into surrounding tissue (*B*), necrosis (*C*), increased mitoses (*D*), and pleomorphic epithelioid (*E*) or spindled (*F*) cells.

Fig. 8. Malignant PEComa with infiltration of surrounding soft tissue (*A*), brisk mitotic activity (*B*), and pleomorphic, multinucleated giant cells (*C*). The tumor is positive for HMB45 (*D*), negative for S100 protein (*E*), and shows patchy expression of smooth muscle actin (*F*).

Table 2
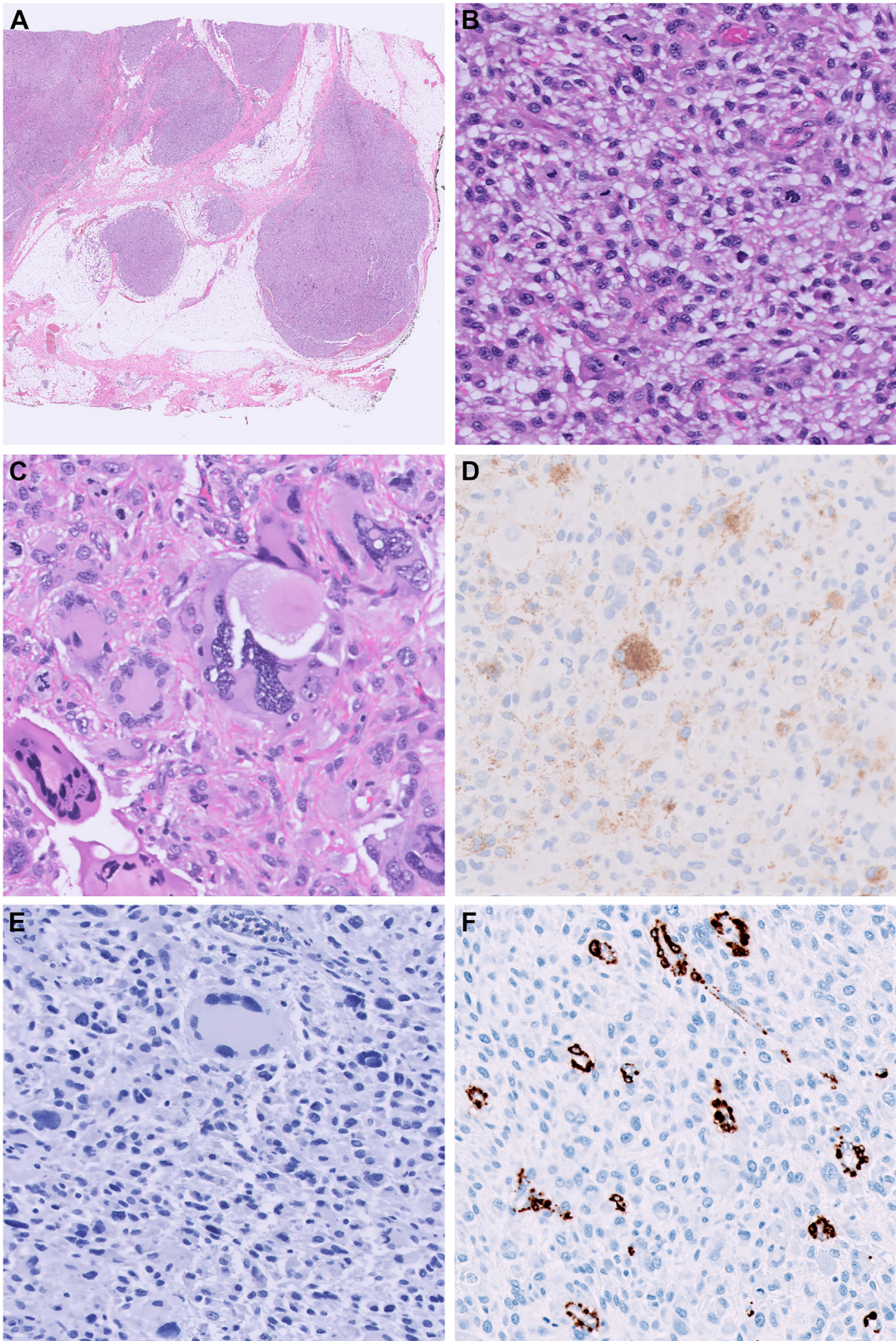**IHC and molecular characteristics of differential diagnostic considerations for epithelioid predominant perivascular epithelioid cell tumors**

Diagnosis	IHC	Molecular Aberration
Metastatic carcinoma	Positive: cytokeratins (diffuse) Negative: melanocytic markers	
Metastatic melanoma	Positive: S100 (diffuse), Sox10 (diffuse) Negative: muscle markers	*BRAF* mutation
Clear cell sarcoma	Positive: S100 (diffuse), Sox10 (diffuse) Negative: muscle markers	*EWSR1-ATF1* or *EWSR-CREB1* fusions
Rhabdomyosarcoma	Positive: myogenin, myoD1, Pax7 Negative: melanocytic markers	*FOXO1* rearrangements in alveolar subtype
Epithelioid sarcoma/ malignant rhabdoid tumor	Positive: cytokeratins, EMA, CD34 Negative: INI1 (lost)	*hSNF5/INI1/SMARCB1* mutation testing
Epithelioid mesothelioma	Positive: cytokeratins, EMA, calretinin, WT1 Negative: melanocytic markers	
Lymphoma or plasma cell neoplasm	Positive: CD45 Negative: melanocytic and muscle markers	Variable[a]
Epithelioid angiosarcoma	Positive: CD31, ERG, CD34 Negative: melanocytic and muscle markers	
TFE3-rearranged neoplasms		
Alveolar soft part sarcoma	Negative: melanocytic markers	*ASPSCR1-TFE3* fusion
Metastatic Xp11.2 renal cell carcinoma	Positive: cytokeratins, PAX8 Negative: melanocytic markers, cathepsin K	Various *TFE3* and *TFEB* translocations
Metastatic melanotic Xp11 translocation renal cancers	Similar to *TFE3*-rearranged PEComas	Similar to *TFE3*-rearranged PEComas

[a] Targeted NGS panels are available for suspected hematolymphoid malignancies.

TP53 mutations may also portend malignancy in PEComas,[19,44,53] and PEComas in patients with LFS may behave aggressively.[54,55]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for PEComas is broad, and largely guided by the predominant histologic component and tumor location. An IHC panel is most useful and could be supplemented by molecular studies if necessary (**Tables 2–4**).

Given the expression of melanocytic markers, PEComas are frequently confused with metastatic melanoma or clear cell sarcoma[23] due in part to overlapping morphology, including epithelioid to spindled cells with prominent nucleoli and multinucleated cells and occasional pigmentation.[23]

These can usually be distinguished using IHC (see **Table 2**). Diffuse S100 expression is supportive of melanoma, which is generally negative or focal/weak in PEComas.[1] SOX10 is positive in the majority of melanoma and negative in PEComa.[10] If ambiguity remains, molecular studies may be helpful (see **Table 2**). PEComas with predominantly epithelioid morphology can also be confused with carcinomas, especially when located in visceral sites, rhabdomyosarcoma, epithelioid sarcoma, and epithelioid mesothelioma.

Spindle-predominant PEComas may be confused with smooth muscle neoplasms (see **Table 3**). In contrast to PEComas, smooth muscle neoplasms show diffusely eosinophilic cytoplasm, perinuclear vacuoles, and "cigar-shaped" nuclei.[23]

Table 3
IHC and molecular characteristics of differential diagnostic considerations for spindled predominant perivascular epithelioid cell tumors spindled predominant morphology

Diagnosis	IHC	Molecular Aberrations
Leiomyoma	Negative: melanocytic markers	
Leiomyosarcoma	Negative: Melan-A	
Gastrointestinal stromal tumor	Positive: DOG1 (diffuse), CD117 (diffuse), CD34, smooth muscle actin (focal) Negative: melanocytic markers, desmin	*KIT, PDGFRA* mutation testing

Leiomyosarcoma tends to have more cytologic atypia, frequent mitosis, and necrosis. Leiomyosarcomas may occasionally express HMB45[59] and cathepsin K; however, Melan-A is predictably negative.[10] Given inconsistencies in immunohistochemical profile, a panel of immunostains including HMB45, Melan-A, SMA, and desmin is recommended.[23] In the gastrointestinal tract, gastrointestinal stromal tumor (GIST) may enter the differential diagnosis. Because PEComas can rarely be positive for CD117,[1] GIST should be excluded with DOG1, a more specific stain. Finally, in the rare event of fat-predominant soft tissue PEComas (extrarenal AMLs), a variety of lipomatous tumors enter the differential and can be distinguished using a panel of IHC and molecular studies (see **Table 4**).

Given the occasional ambiguities in immunohistochemical staining patterns, molecular profiling has become increasingly important in distinguishing PEComas from other mesenchymal lesions with overlapping immunophenotypic profile,[60] with *TSC1* or *TSC2* alterations lending strong support for the diagnosis of PEComa in the appropriate morphologic context. When considering the diagnosis of

PEComa, the detection of a *TFE3* rearrangement, while helpful, raises additional differential considerations of other *TFE3*-rearranged neoplasms, including Xp11.2 RCC, melanotic Xp11 translocation renal cancers, and alveolar soft part sarcoma (ASPS), which can also show alveolar or nested architecture, clear or eosinophilic cytology, immunoreactivity for TFE3, and *TFE3* rearrangements by FISH. Although metastatic Xp11.2-associated renal cancers are readily distinguished using IHC (see **Table 2**), melanotic Xp11 translocation renal cancers bear much greater similarity to PEComas in that they are usually positive for melanocytic markers and cathepsin K, whereas negative for PAX8 and muscle markers and most commonly involve an *SFPQ::TFE3* translocation[61]; hence, extrarenal soft tissue metastases of melanotic Xp11 translocation renal cancers may be virtually indistinguishable from soft tissue PEComas based on pathologic features alone. ASPS usually occurs in deep soft tissue sites of the extremities and more frequently shows vascular space invasion; unlike most *TFE3*-rearranged PEComas, ASPS is negative for HMB45 and Melan-A. Interestingly, ASPS harbors a unique

Table 4
IHC and molecular characteristics of differential diagnostic considerations for fat-predominant perivascular epithelioid cell tumors

Diagnosis	IHC	Molecular Aberrations
Lipoma	Negative: melanocytic markers	
Spindle cell lipoma	Positive: CD34 (diffuse) Negative: RB1 (loss) melanocytic markers, muscle markers	*RB1* mutation
Liposarcoma	Positive: MDM2 Negative: melanocytic markers	*MDM2, CDK4* amplifications

ASPSCR1::TFE3 translocation, which is strongly associated with ASPS and not typically found in PEComas, hence useful in their distinction.[22] However, the *ASPSCR1::TFE3* translocation was recently reported in three PEComa-like tumors expressing muscle markers,[62] suggesting that *TFE3*-rearranged neoplasms may lie on a continuum and our understanding of their distinctions is still evolving.

SUMMARY

PEComas arising in soft tissue are rare, constituting only a small subset of the complex PEComa family. Most present outside of the TSC context, but a minority appear to be associated with TSC. Although PEComas are unified by a distinctive perivascular growth, they have a diverse histologic spectrum with wide-ranging morphologic mimics. Their distinctive myomelanocytic immunophenotype has been a mainstay of PEComa diagnoses; however, molecular characterization, both of *TSC* alterations and *TFE3* rearrangements, is becoming a more common diagnostic tool in ambiguous cases. The increasingly widespread adoption of molecular sequencing, conversely, is challenging previously drawn boundaries between different diagnostic entities, especially among *TFE3*-rearranged neoplasms. Importantly, our understanding of the relationship between these dichotomous molecular pathways and how they may relate to the biology and prognosis of these tumors is still evolving.

DISCLOSURE

The authors have nothing to disclose.

CLINICS CARE POINTS

- PEComas are rare but increasingly recognized tumors with wide-ranging clinical behaviors that can be unpredictable.
- Distinguishing PEComas from melanocytic or smooth muscle neoplasms can be challenging and may involve a panel of immunohistochemical markers and possibly molecular studies.
- Evaluation for TFE3 rearrangements in PEComas can be important, particularly in aggressive cases, due to the potential of resistance to mTOR inhibition.

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