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ORIGINAL PAPER

Pericyte antigens in angiomyolipoma and PEComa family tumors

Jia Shen[1] · Swati Shrestha[1,2] · Yu-Hsin Yen[1,2] · Michelle A. Scott[3] · Greg Asatrian[1] · Raymond Barnhill[2,6] · Claire Lugassy[2,6] · Chia Soo[4,5] · Kang Ting[1] · Bruno Peault[4,7] · Sarah M. Dry[2] · Aaron W. James[1,2,4]

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Abstract Perivascular epithelioid cell tumors (PEComas) are an uncommon family of soft tissue tumors with dual myoid–melanocytic differentiation. Although PEComa family tumors commonly demonstrate a perivascular growth pattern, pericyte antigen expression has not yet been examined among this unique tumor group. Previously, we demonstrated that a subset of perivascular soft tissue tumors exhibit a striking pericytic immunophenotype, with diffuse expression of αSMA, CD146, and PDGFRβ. Here, we describe the presence of pericyte antigens across a diverse group of PEComa family tumors ($n = 19$ specimens). Results showed that pericyte antigens differed extensively by histological appearance. Typical angiomyolipoma (AML) specimens showed variable expression of pericyte antigens among both perivascular and myoid-appearing cells. In contrast, AML specimens with a predominant spindled morphology showed diffuse expression of pericyte markers, including αSMA, CD146, and PDGFRβ. AML samples with predominant epithelioid morphology showed a marked reduction in or the absence of immunoreactivity for pericyte markers. Lymphangiomyoma samples showed more variable and partial pericyte marker expression. In summary, pericyte antigen expression is variable among PEComa family tumors and largely varies by tumor morphology. Pericytic marker expression in PEComa may represent a true pericytic cell of origin, or alternatively aberrant pericyte marker adoption. Markers of pericytic differentiation may be of future diagnostic utility for the evaluation of mesenchymal tumors, or identify actionable signaling pathways for future therapeutic intervention.

Keywords CD146 · PDGFRB · Mel-CAM · Platelet-derived growth factor receptor · PEComa · Angiomyolipoma

Jia Shen and Swati Shrestha share equally in the work presented herein.

✉ Aaron W. James
Awjames@mednet.ucla.edu; aaronwjames1@gmail.com

1 Division of Growth and Development, School of Dentistry, University of California, Los Angeles, CA, USA

2 Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, 10833 Le Conte Ave., 13-145 CHS, Los Angeles, CA 90095, USA

3 Nationwide Children's Hospital, Columbus, OH, USA

4 Orthopedic Hospital Research Center, University of California, Los Angeles, CA, USA

5 Department of Surgery, University of California, Los Angeles, Los Angeles, CA, USA

6 Institut Curie, Paris, France

7 Center for Regenerative Medicine, University of Edinburgh, Edinburgh, UK

Introduction

The perivascular epithelioid cell tumor (PEComa) family of tumors includes a group of anatomically and histologically diverse neoplasms with dual myoid–melanocytic differentiation [1]. The most commonly encountered PEComa family tumor is angiomyolipoma (or AML), which occurs predominantly in the kidney or liver [2], and has a characteristic triphasic histological appearance including thick-walled blood vessels, myoid-appearing perivascular cells, and lipid-distended cells resembling adipocytes [1]. On occasion, a predominant myoid component overshadows the vascular or

lipid-filled components, which can have a predominant spindled or epithelioid cytomorphology. Of these, epithelioid AML has been shown to have an aggressive clinical behavior [3], and a proposed risk stratification has been previous put forth [4]. Lymphangiomyoma, lymphangiomyomatosis, and clear cell sugar tumor (CCST) are rare, distinct entities that have been well described [5, 6]. PEComas of other sites, including soft tissue and gynecologic origin, have been well documented [7], while other sites are more unusual [8–11]. Immunohistochemical features of PEComa family tumors are distinct and typically show co-expression of α-smooth muscle actin (αSMA) and melanocytic markers [12], demonstrating a dual myoid–melanocytic immunophenotype. HMB-45 appears to be the most sensitive marker (96 %), followed by Melan-A, MiTF, and S100 expression [7]. Despite the perivascular growth pattern that defines PEComa family tumors, the expression of pericytic markers in PEComa is essentially unknown.

Pericytes are mesenchymal cells that closely enwrap small blood vessels, regulating and supporting the microvasculature through direct contact with the endothelium. Pericytes demonstrate a distinct antigen expression, including co-localization of αSMA, CD146, and PDGFRβ (platelet-derived growth factor receptor β) [13, 14]. In addition, pericytes lack endothelial differentiation (including lack of CD31 and CD34 antigen expression) [13, 14]. We recently reported a uniform pericytic immunophenotype of the closely related soft tissue perivascular tumors, including glomus tumor, myopericytoma, and angioleiomyoma [15]. Here, diffuse immunoreactivity for αSMA, CD146, and PDGFRβ was seen, suggestive of pericytic differentiation within this tumor group [15]. Recently, Siroky et al. [16] examined renal AML among patients with tuberous sclerosis complex, finding expression of pericyte markers including ANG II type I receptors, PDGFRβ, αSMA, and VEGF receptor 2. However, a more comprehensive examination of pericyte markers in PEComa family tumors has not been performed.

In the present study, pericytic antigen expression was observed in a spectrum of PEComa family tumors—which was largely predictable based on cytomorphology. Typical angiomyolipomas (AMLs) with triphasic differentiation showed reliable pericyte antigen expression. Strikingly, AML with spindled morphology showed stronger and more diffuse pericyte marker expression, while AML with predominant epithelioid morphology showed reduced or absent pericyte marker expression. These findings are suggestive of pericytic differentiation within select members of the PEComa family tumors, which can be predicted based on cytomorphologic appearance. Whether this represents true pericytic cell origins or rather aberrant adoption of pericytic marker expression is uncertain.

Materials and methods

Histology and immunohistochemistry

Tumors were identified using a retrospective chart review of the pathology tissue archives of the Department of Pathology and Laboratory Medicine at the University of California, Los Angeles (UCLA) using the search terms "angiomyolipoma, perivascular epithelioid cell tumor, and PEComa." Slides were reviewed by two independent pathologists to ensure accuracy of diagnosis (S.M.D and A.W.J.). On re-review, tumors were assigned to one of five categories: (1) "typical" AML which demonstrated a characteristic triphasic histological appearance, (2) AML with predominant spindled cytomorphology (samples were combined under this designation which showed predominant spindled tumor cells and with minimal lipid-laden cells), (3) AML with predominant epithelioid cytomorphology (epithelioid AMLs were defined as those tumors with predominant epithelioid cytomorphology of tumor cells and with minimal lipid-laden component), (4) malignant AML, and (5) lymphangiomyoma according to previously published diagnostic criteria (1). Recognizing that agreement does currently not exist regarding criteria for malignancy in AML, we chose the criteria set forth by Brimo et al. to distinguish malignant potential in renal angiomyolipoma [17]. Briefly, a designation of malignant AML was given when three of the following four criteria were present: (1) ≥70 % atypical epithelioid cells, (2) ≥2 mitoses per 10 HPF, (3) the presence of atypical mitotic figures, and (4) the presence of necrosis. Patient information was obtained, including age, sex, tumor location, tumor size, and previous immunohistochemical stains performed during the initial diagnostic evaluation. Formalin-fixed paraffin-embedded (FFPE) tumor tissue from patients was acquired from the tissue archives, under UCLA IRB approval # 13-000918.

Immunohistochemistry for pericyte markers was performed using the ABC method (Vectastain Elite ABC, Vector Laboratories, Burlingame, CA, USA) using DAB as the chromogen (ImmPACT DAB, Vector Laboratories). Multiple antigens were detected by multiplexing the ABC method and DAB chromogen with an alkaline phosphatase polymer detection method (ImmPress-AP Polymer Detection, Anti-mouse IG, Vector Laboratories) and Vector Red® chromogen (Vector Red® Alkaline Phosphatase Substrate, Vector Laboratories).

The following primary antibodies were used: monoclonal rabbit anti-CD146 (1/500, EPR3208, ABCAM, Cambridge, MA, USA), monoclonal mouse anti-αSMA (1/75, [1A4], ABCAM), monoclonal rabbit anti-PDGFRβ (1/100, [2E8E1], Cell Signaling Technologies), monoclonal

mouse anti-HMB-45 ([M0634], Dako North America, Inc., Carpinteria, CA, USA), and monoclonal mouse anti-Melan-A ([CM0077B], Biocare Medical). The following secondary antibodies were used: polyclonal goat biotinylated anti-rabbit IgG (1/500, Sigma, St. Louis, MO, USA), polyclonal horse anti-mouse IgG (1/500, [H + L], Vector Laboratories), and polyclonal goat anti-rat Ig (1/500, Becton–Dickinson and Company).

Heat-mediated antigen retrieval was performed for all immunohistochemical stains in 1 mM tris–EDTA, 0.01 % Tween-20 (Sigma), pH 8. Non-specific antibody binding was blocked (IHC-TEK Antibody Diluent, pH 7.4, IHC World, LLC, Woodstock, MD, USA). Endogenous peroxidase and alkaline phosphatase blocking solution was used (BLOXALL Endogenous Peroxidase and Alkaline Phosphatase Blocking Solution, Vector Laboratories). Mayer's hematoxylin was used as a nuclear counterstain (1/5, ABCAM), and slides were mounted using an aqueous media (VectaMount AQ, Vector Laboratories).

Immunohistochemical semiquantitation

Semiquantitative grading of immunohistochemical stains was performed with some modification of previous protocols by three blinded independent observers [18]. Intensity of staining was graded on a three-point scale (0 to 3+), defined as follows: 0 absent stain; 1+ weak, focal cytoplasmic staining or weak, non-contiguous membranous staining; 2+ moderate, focal to diffuse cytoplasmic staining or moderate, partially contiguous membranous staining; and 3+ strong, diffuse cytoplasmic staining or strong, contiguous membranous staining. In cases of disagreement between observers, tumor staining was re-evaluated by the same observers and the majority opinion was selected. In addition, the percentage of tumor cells stained was also evaluated, using a 5 % incremental scale, and averages between observers were calculated. Statistical analysis of semiquantitation was performed when appropriate, using a two-sample Wilcoxon rank-sum (Mann–Whitney) test, using STATA. $P < 0.05$ was considered significant.

Results

Demographics of patients with PEComa tumor samples

Nineteen PEComa specimens were identified in the pathology records. The majority of tumors were from women (84.2 %, 16/19 samples) with a mean age of 54.63 years (range 29–86 years). The majority of tumors were of renal/perirenal origin (68.4 %, 13/19 tumors), while other sites included the retroperitoneum/pelvis ($n = 4$), liver ($n = 1$), and mediastinum ($n = 1$). Mean tumor size was 5.43 cm (range 1.1–13.0 cm). Tumors were commonly positive for melanocytic markers, including HMB45 (94.7 %, 18/19) and MART1 (88.9 %, 8/9). When assessed, smooth muscle markers were also primarily positive, including SMA (81.8 %, 9/11) and desmin (75 %, 3/4). Epithelial markers were uniformly negative when assessed, including pankeratin (0/13), EMA (0/5), and CA9 (0/4). PEComa family tumors were next split into categories based on histological appearance, including those tumors with the typical triphasic appearance (typical angiomyolipoma, $n = 5$), those with predominant spindle cell morphology ($n = 6$), and those with predominant epithelioid morphology ($n = 4$), lymphangiomyoma ($n = 3$), and malignant angiomyolipoma ($n = 1$).

Pericyte marker expression in typical angiomyolipoma

Pericyte markers were first examined in angiomyolipomas (AMLs) (Fig. 1). Pericyte markers were first examined in the vascular component (Fig. 1a–h). αSMA showed strong immunoreactivity in the majority of cells within the thick-walled vessels of AML. Likewise, CD146 and PDGFRβ showed a striking pattern of perivascular immunoreactivity, although this varied somewhat in intensity between tumors. The tumor cells with epithelioid/myoid morphology were next examined (Fig. 1i–p). Here again, strong immunoreactivity for αSMA, CD146, and PDGFRβ was seen. Next, semiquantitation of immunohistochemical staining was performed (Table 1). Strong immunoreactivity for αSMA was observed in all tumors (3+ staining intensity, 5/5 samples) and was widely distributed across all tumor cells (>75 % of tumor cells in 4/5 samples). Of note, distribution was only assessed in the myoid and vascular tumor cells (and excluded the lipid-laden component which showed minimal immunoreactivity for any marker). Likewise, moderate immunoreactivity for CD146 was observed across all tumor samples (2+ intensity, 5/5 samples). In most cases, the majority of tumor cells showed immunoreactivity (≥60 % staining distribution in 3/5 cases; 49 ± 22.75 % mean staining distribution). Weak-to-moderate immunoreactivity for PDGFRβ was seen in all cases (1–2+ intensity, 5/5 samples). In most cases, a large minority of tumor cells demonstrated immunoreactivity (19 ± 19.81 % mean staining distribution).

Pericyte marker expression in AML with spindled morphology

Pericyte markers were next examined in AML specimens with predominant spindle cell morphology (Fig. 2). Results showed AML tumors with predominant spindled morphology

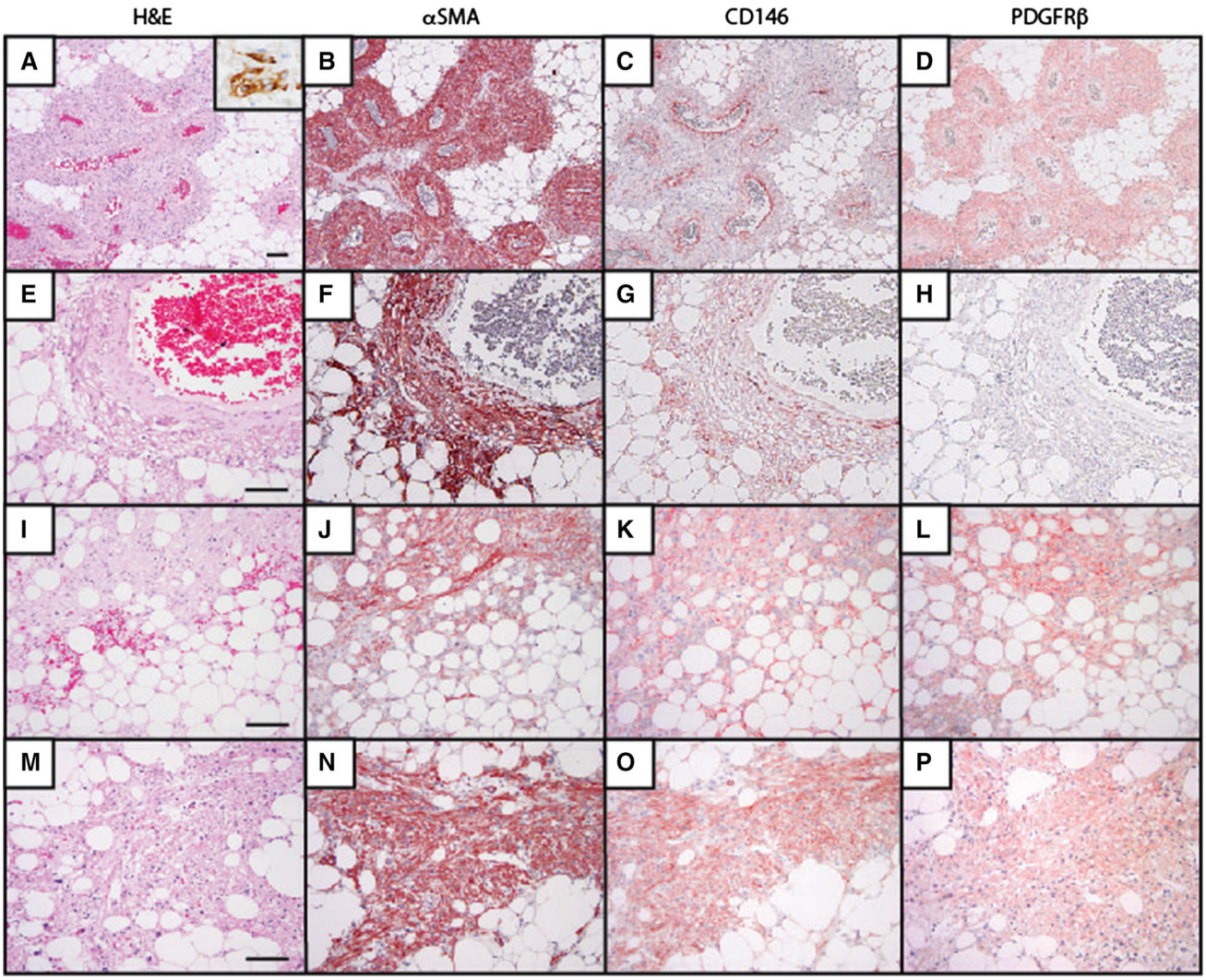

Fig. 1 Pericyte marker expression among angiomyolipoma. Characteristic appearance of angiomyolipoma. **a**–**h** Histological appearance and pericyte markers with emphasis of vascular elements, including **a**, **e** routine H&E staining. **b**, **f** α-Smooth muscle actin (αSMA), **c**, **g** CD146, and **d**, **h** platelet-derived growth factor receptor β (PDGFRβ) immunohistochemical staining. **i**–**p** Histological appearance and pericyte markers with emphasis of myoid elements, including **i**, **m** routine H&E staining. **j**, **n** α-Smooth muscle actin (αSMA), **k**, **o** CD146, and **l**, **p** platelet-derived growth factor receptor β (PDGFRβ) immunohistochemical staining. *Inset depicts* representative HBM45 immunoreactivity. *Black scale bar* 50 μm

Table 1 Summary of pericyte markers across PEComa family tumors

Tumor type (*n*)	αSMA intensity	αSMA distribution (%)	CD146 intensity	CD146 distribution (%)	PDGFRβ intensity	PDGFRβ distribution (%)
Typical AML (5)	3 (±0)	73 (±24.89)	2 (±0)	49 (±22.75)	1.6 (±0.55)	19 (±19.81)
Spindled AML (6)	3 (±0)	92.5 (±4.18)	2 (±0)	77.5 (±9.35)	1.67 (±1.03)	36.7 (±22.73)
Epithelioid AML (4)	1 (±1.15)	18.75 (±28.39)	0.5 (±0.58)	25 (30)	0 (±0)	0 (±0)
Malignant AML (1)	2	35	2	40	0	0
Lymphangiomyoma (3)	2.33 (±0.58)	51.67 (±43.12)	0.67 (±0.58)	20 (±17.32)	0 (±0)	0 (±0)

had increased expression of pericyte markers, including αSMA, CD146, and PDGFRβ. Strong immunoreactivity for αSMA was observed in all tumors (3+ staining intensity, 6/6 samples) and was widely distributed across all tumor cells (>85 % of tumor cells in 6/6 samples). Likewise, moderate immunoreactivity for CD146 was observed across all samples

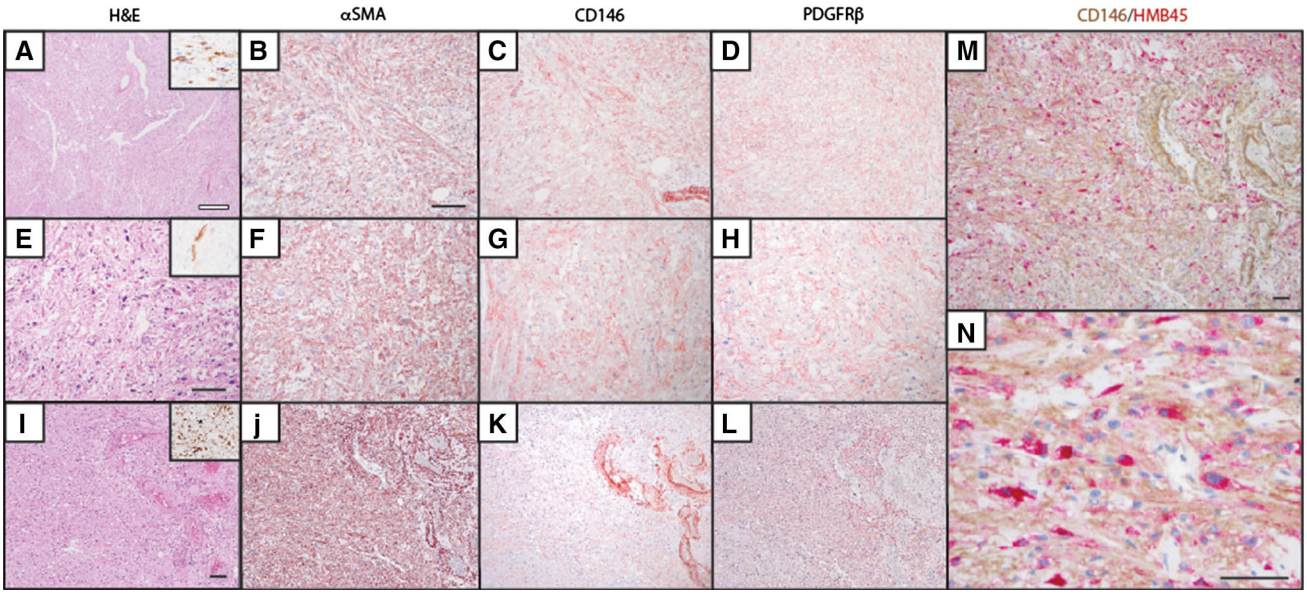

Fig. 2 Pericyte marker expression among AML with spindled morphology. Histological appearance and pericyte markers within AML with predominant spindle cell morphology, by **a**, **e**, **i** routine H&E staining, **b**, **f**, **j** αSMA, **c**, **g**, **h** CD146, and **d**, **h**, **l** PDGFRβ immunohistochemical staining. **m**, **n** Pericyte and melanocytic marker co-expression, as demonstrated by coexpression of CD146 (*brown*) and HMB45 (*red*). *Inset depicts* representative HBM45 immunoreactivity. *Black scale bar* 50 μm. *White scale bar* 200 μm

(2+ intensity, 6/6 samples). In all cases, the majority of tumor cells showed immunoreactivity (≥60 % staining distribution in 6/6 cases; 77.5 ± 9.35 % mean staining distribution). Variable immunoreactivity for PDGFRβ was seen in most cases (1–3+ intensity, 5/6 samples). In most cases, a large minority of tumor cells demonstrated immunoreactivity (36.7 ± 22.73 % mean staining distribution). Co-expression of pericyte and melanocytic markers was next assessed (Fig. 2m, n). Here, co-expression of CD146 and HBM45 confirmed the dual pericytic/melanocytic antigen expression.

A minority of cases showed prominent sclerosis with or without calcification (Fig. 3, sclerotic AML). Immunoreactivity for αSMA and CD146 was relatively similar between spindle cell PEComas with or without sclerosis (Fig. 3b–g). Of note, a reduction in both the intensity and distribution of PDGFRβ immunoreactivity was among spindle cell AML tumors with sclerosis (Fig. 3d, h).

Pericyte marker expression in AML with epithelioid morphology

Next, pericyte markers were examined across AML with predominant epithelioid morphology (Fig. 4). Strikingly, a reduction in or the absence of pericyte markers was observed in most tumor cells, including αSMA, CD146, and PDGFRβ. Instead, pericyte markers highlighted intralesional blood vessels only, as well as some weak staining in the fibrous stroma. Moderate αSMA immunoreactivity was seen in half of samples and in the minority of tumor cells (18.75 ± 28.39 % staining distribution). Weak CD146 immunostaining was observed in half of samples. PDGFRβ immunoreactivity was not seen across any epithelioid AML (0/4 samples).

Pericyte marker expression in other PEComa family tumors

One AML demonstrated features consistent with malignancy, including an increased mitotic rate, atypical mitotic figures, and tumor necrosis (Fig. 5a–d). Moderate staining intensity for both αSMA and CD146 was seen in a large minority of tumor cells (2+ intensity, 35–40 % distribution).

Finally, the intensity and distribution of pericyte markers in lymphangiomyoma were examined. Pericyte markers showed variable expression across lymphangiomyoma samples (Fig. 5e–h). Tumors demonstrated moderate-to-strong αSMA immunoreactivity (2–3+ intensity) with a wide range of staining distribution (5–90 % distribution across 3/3 samples). Weak CD146 immunoreactivity was noted in the majority of samples (1+, 2/3 samples). PDGFRβ immunostaining was not seen across lymphangiomyoma samples.

In summary, expression of pericyte markers in PEComa specimens largely correlates with tumor cytomorphology. Angiomyolipomas with typical triphasic morphology showed characteristic pericyte marker expression, predominantly in the myoid-appearing perivascular epithelioid

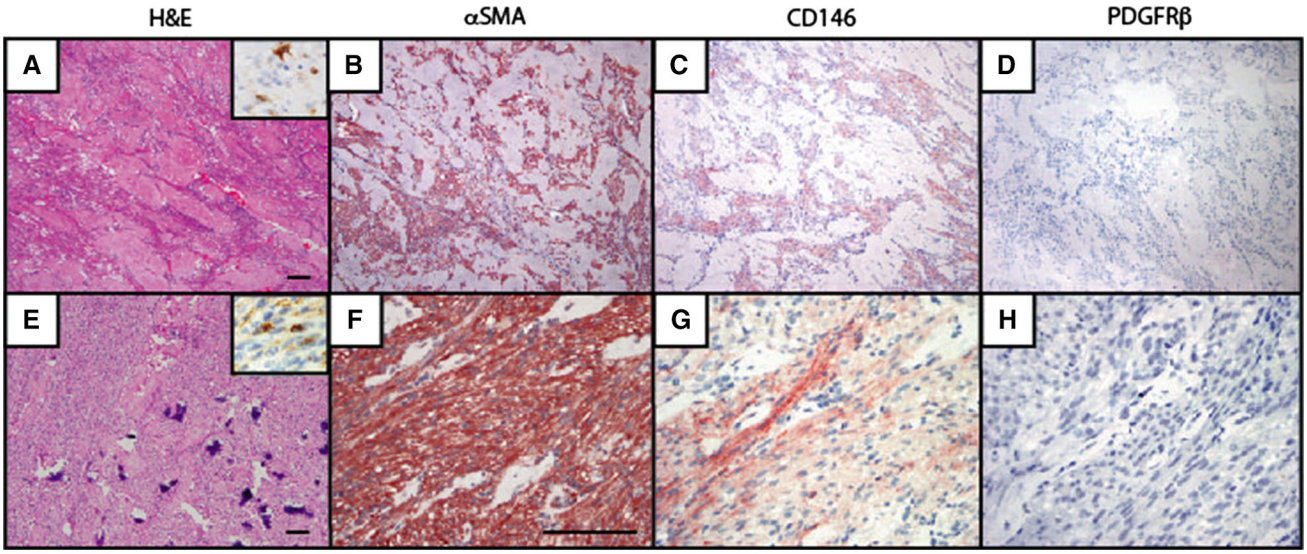

Fig. 3 Pericyte marker expression among AML with prominent sclerosis. Histological appearance and pericyte markers within AML with prominent sclerosis, by **a**, **e** routine H&E staining, **b**, **f** αSMA, **c**, **g** CD146, and **d**, **h** PDGFRβ immunohistochemical staining. *Inset* *depicts* representative HBM45 immunoreactivity. Of note, both tumors showed a predominant spindle cell morphology. *Black scale bar* 50 μm

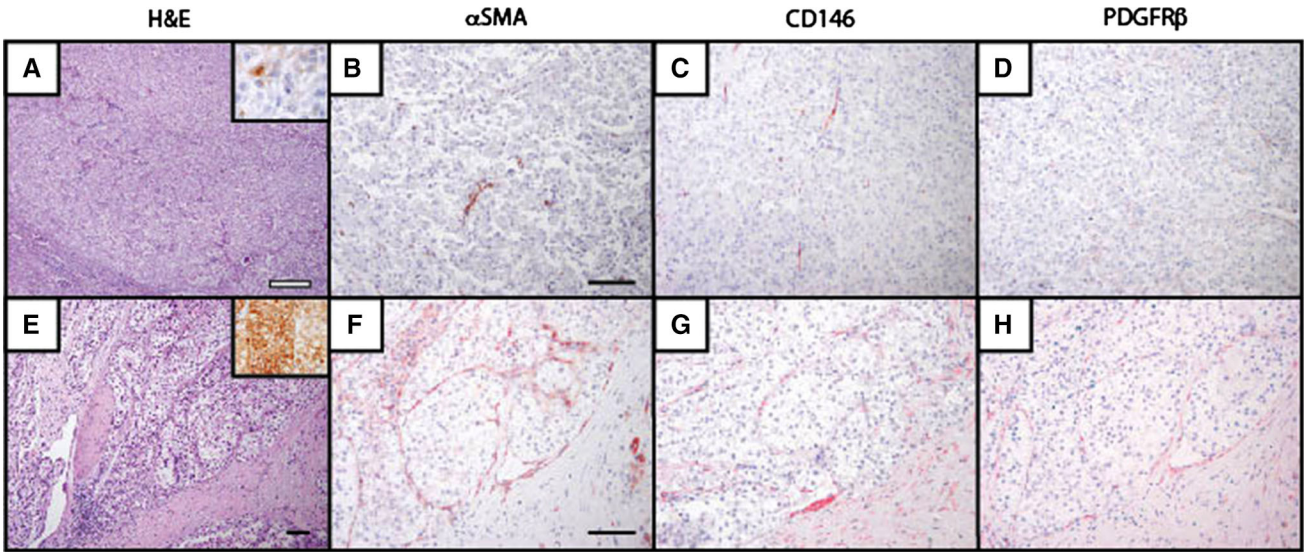

Fig. 4 Pericyte marker expression among AML with epithelioid morphology. Histological appearance and pericyte markers within AML with predominant epithelioid morphology, by **a**, **e** routine H&E staining, **b**, **f** αSMA, **c**, **g** CD146, and **d**, **h** PDGFRβ immunohistochemical staining. *Inset* **a** depicts representative MelanA, while other insets depict HBM45 immunoreactivity. *Black scale bar* 50 μm. *White scale bar* 200 μm

tumor cells. Strong and diffuse pericyte marker expression was identified in PEComa tumors with predominant spindle cell cytomorphology. In contrast, those samples with a predominant epithelioid appearance had a notable paucity of pericyte marker expression. Lymphangiomyoma samples showed more variable and partial pericyte marker expression.

Discussion

The present study extends our previous findings, in which we identified diffuse expression of pericyte markers among a subset of soft tissue tumors with perivascular tumor growth [15]. In our previous study, we examined pericyte markers across a group of related tumors including glomus

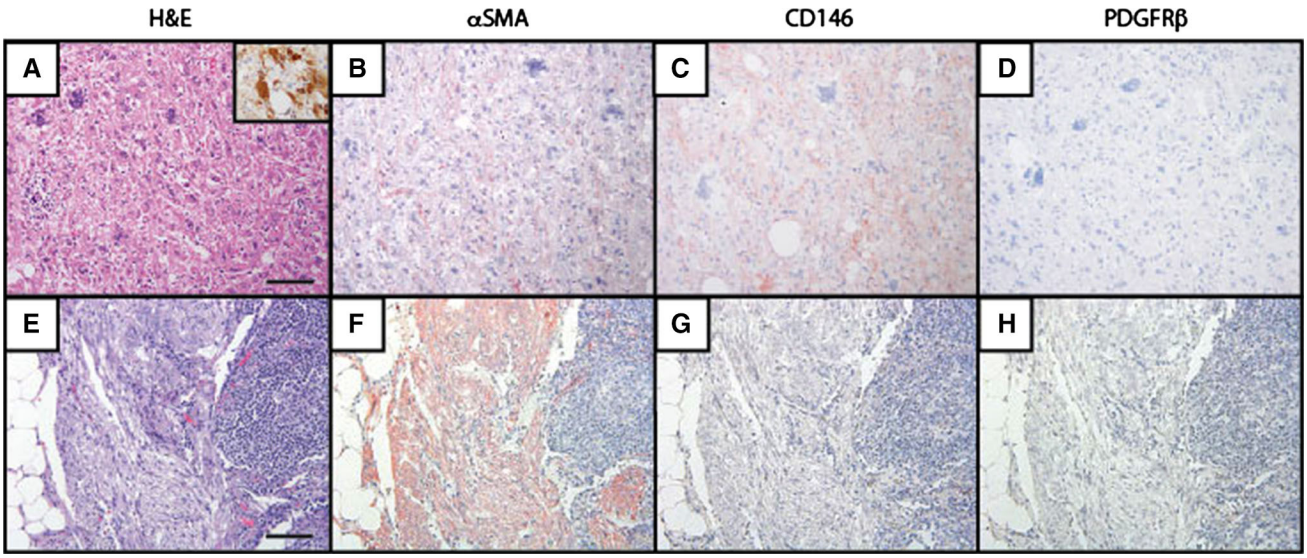

Fig. 5 Pericyte marker expression among other PEComa family tumors. **a** Histological appearance of malignant AML, by routine H&E staining. **b–d** Pericyte markers in malignant AML, to include **b** αSMA, **c** CD146, and **d** PDGFRβ immunohistochemical staining. **e** Histological appearance of lymphangiomyoma, by routine H&E staining. **f–h** Pericyte markers in lymphangiomyoma, to include **f** αSMA, **g** CD146, and **h** PDGFRβ immunohistochemical staining. *Inset depicts* representative HBM45 immunoreactivity. *Black scale bar* 50 μm

tumor, myopericytoma, and angioleiomyoma. All tumors showed diffuse and replicable immunoreactivity for pericyte markers, including αSMA, CD146, and PDGFRβ [15]. In comparison with these tumors, PEComa family tumors show more variable pericyte marker expression that is highly dependent on tumor morphology.

One of the main and somewhat unexpected findings was the marked difference in pericyte markers between AML with spindled versus those with epithelioid cytomorphology. As mentioned, the intensity and distribution of all pericyte markers were significantly reduced in epithelioid AML. Although incompletely understood, epithelioid AMLs tend to behave in a more aggressive fashion than spindled AML [3, 4]. Perhaps the reduction in or the absence of pericyte markers in epithelioid AML reflects a relative loss of pericyte differentiation that accompanies a more aggressive tumor behavior.

Importantly, no known pericytic markers are absolutely specific, and additional pericyte markers have yet to be examined in details. Despite these limitations, the combination of αSMA+ CD146+ PDGFRβ+ is specific for pericytic and/or smooth muscle differentiation. CD146 is also expressed in endothelium, smooth muscle, and Schwann cells [19]. Similarly, PDGFRβ is also in diverse cell types including fibroblasts, endothelium, and smooth muscle [20]. With this diverse expression profile, it is understandable that these markers are seen in multiple tumors. Nevertheless, the combination of αSMA+ CD146 + PDGFRβ+ appears specific for pericytic and/or smooth muscle differentiation. Other potentially more specific pericyte markers have yet to be investigated in tumors, including NG2 [21–23], RGS5 [24, 25], Ang-1 [26], and nestin [27, 28].

Recent evidence suggests that common tumors of the brain, pancreas, prostate, and skin adopt a pericyte phenotype in order to spread along the abluminal surfaces of vessels. This tumor pathway has been termed pericytic mimicry and/or extravascular migratory metastasis (EVMM). During extravascular migration, angiotropic tumor cells migrate along the abluminal vascular surfaces of vessels in a pericyte location for microvessels, in a smooth muscle cell or adventitial cell location for larger vessels. Angiotropic tumor cells are defined histologically as tumor cells closely associated with the endothelium of vascular channels in a pericytic location, are generally detected at the advancing front of the tumor, and do not show intravasation into the blood vessel. This under recognized route of tumor spread is most well documented in melanoma. Through this pathway, melanoma cells may spread to nearby or more distant sites. Angiotropism is a prognostic factor predicting risk for metastasis in human melanoma and a marker of EVMM in several experimental models. [29–32]. Similarly, in the malignant brain tumor glioblastoma multiforme, tumor cells adopt a pericyte-like location associated with perivascular invasion [33–35]. In fact, using cell-tracking techniques, it has been shown that the majority of vessel-lining pericyte-like cells in glioblastoma are actually of tumor cell origin. Likewise, recent research suggests that pancreatic and prostatic adenocarcinoma exhibit pericytic mimicry leading to regional

invasion and/or EVMM [36, 37]. Previous studies have demonstrated that angiotropic melanoma cells may show aberrant expression of pericyte antigens such as CD146 and PDGFRβ [30]. However, further studies are needed to define the precise immunophenotype of tumor cells involved in pericytic mimicry, and the links between this phenomenon and the phenotype we observed within PEComa family tumors.

In summary, these findings clearly support pericytic marker expression in PEComa family tumors, which can be largely predicted by cytomorphology. While typical angiomyolipoma and AML with spindle cell morphology show diffuse expression of pericytic antigens, epithelioid AML specimens and lymphangiomyoma do not. Markers of pericytic differentiation may be of future diagnostic utility for the evaluation of mesenchymal tumors or identify actionable signaling pathways for future therapeutic intervention.

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Compliance with Ethical Standards

Conflict of interest None.

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