Journal of Orthopaedics 14 (2017) 154–160

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Original Article

Ang-1 and Ang-2 expression in angiomyolipoma and PEComa family tumors

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ARTICLE INFO

Article history:
Received 5 September 2016
Accepted 5 December 2016
Available online

Keywords:
Angiopoietin
Perivascular epithelioid cell tumor
Angiomyolipoma
Pericyte
PEComa
Lymphangiomyoma

ABSTRACT

Objective: Perivascular epithelioid cell tumors (PEComa) are an uncommon family of soft tissue tumors. Previously, we described that the presence of pericyte antigens among PEComa family tumors differs extensively by histologic appearance.
Methods: Here, we extend our findings using the pericyte antigens Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2), using immunohistochemical detection in human tumor samples.
Results: While Ang-1 showed no expression across any PEComa family tumor, Ang-2 showed expression that like other pericyte markers was largely determined by cytologic appearance.
Conclusion/implications: Pericytic marker expression in PEComa may represent a true pericytic cell of origin, or alternatively aberrant pericyte marker adoption.

1. Introduction

The perivascular epithelioid cell tumor (PEComa) family of tumors include a group of anatomically and histologically diverse neoplasms with dual myoid-melanocytic differentiation.[1] The most common PEComa family tumor is angiomyolipoma (or AML), which occurs predominantly in the kidney or liver, and has a characteristic triphasic histologic 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 either a spindled or epithelioid cell morphology. Of these, epithelioid AML has been shown to have an aggressive clinical behavior.[2] Lymphangiomyoma, lymphangiomyomatosis, and clear cell sugar tumor (CCST) are rare, distinct entities.[3] PEComas of other sites, including soft tissue and gynecologic origin have been well documented,[4] while diverse sites have been described. Immunohistochemical features of PEComa family tumors are distinct, and typically show co-expression of smooth muscle markers and melanocytic markers.[5]

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, PDGFRβ (platelet-derived growth factor receptor β), and RGS5.[6,7] Previously, we described the presence of pericyte antigens across a diverse group of PEComa family tumors.[8] Results showed that pericyte antigens differed extensively by histologic 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 or absence of immunoreactivity for pericyte markers.

Angiopoietin proteins are known to play an important role in angiogenesis and vascularization through the Tie2 pathway.[9] Angiopoietin-1 (Ang-1) is produced by pericytes,[10] and is hypothesized to be involved in the reciprocal communication between pericytes and endothelium. Angiopoietin-2 (Ang-2) is mainly expressed in the endothelium but also in pericytes,[10] and appears

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http://dx.doi.org/10.1016/j.jor.2016.12.001
0972-978X/

to increase tumor vascularization and regulate angiogenesis.[11] Ang-2 has well described antagonistic functions on Ang-1/Tie2 signaling in the endothelium.[12] These antagonistic functions of Ang-2 may be cell specific, and in mesenchymal cells Ang-2 antagonism of Ang-1/Tie2 signaling may not occur.[13]

Angiopoietin/Tie signaling has primarily been interrogated in human vascular tumors. Buehler et al. found Ang-1 expression in the majority of angiosarcoma specimens, while Ang-2 expression was found in 42% of tumors.[14] Further, increased Ang-1 expression by immunohistochemical detection correlated with improved overall survival in angiosarcoma.[14] To the best of our knowledge, the expression of angiopoietin family members in PEComa family tumors has not yet been reported. In the present study, we examined the expression of Ang-1 and Ang-2 by immunohistochemical detection across a large set of PEComa family tumors.

2. Materials and methods

2.1. 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 histologic 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 AML 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.[15] Briefly, a designation of malignant AML was given when three of the following four criteria were present: (1) $\geq$70% atypical epithelioid cells, (2) $\geq$2 mitoses per 10 HPF, (3) presence of atypical mitotic figures, and (4) presence of necrosis. Patient information was obtained, including age, sex, tumor location, tumor size, and previous immunohistochemical stains performed during the initial

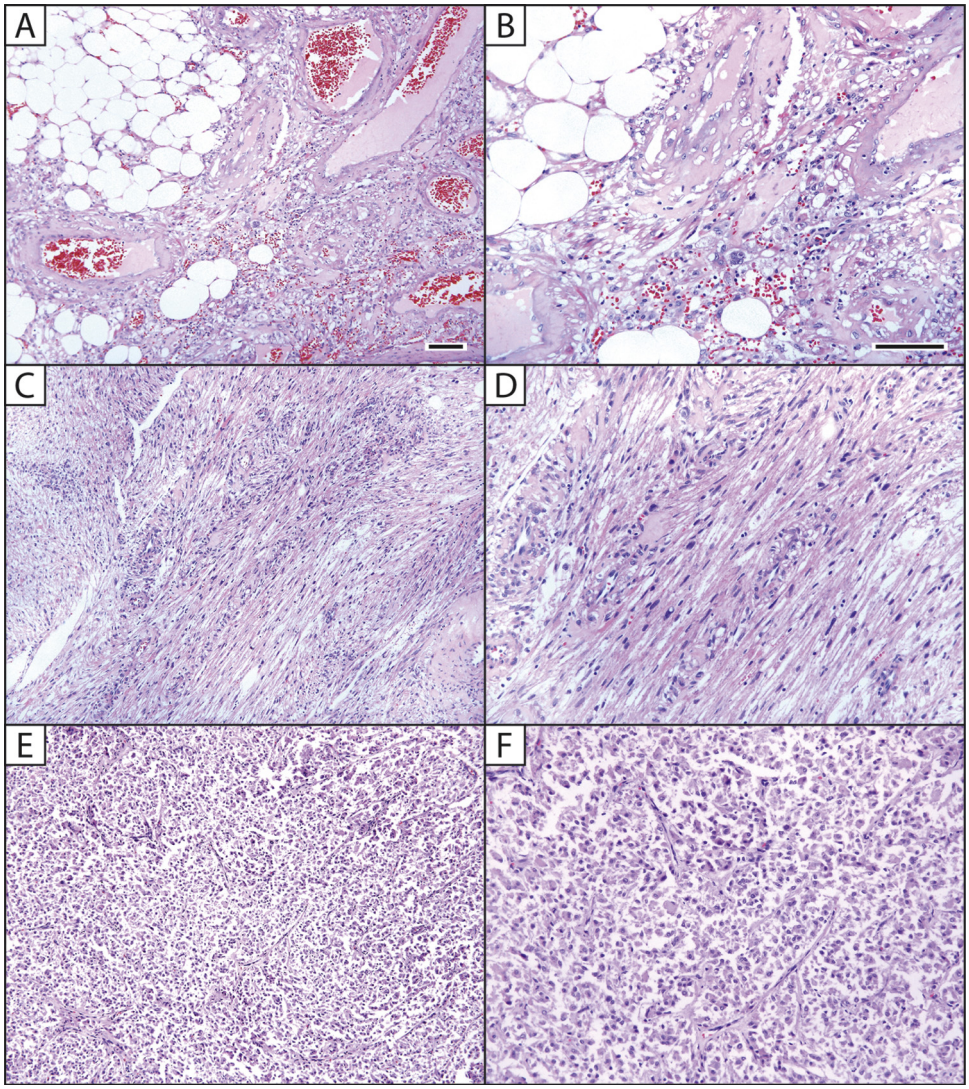

Fig. 1. Typical histologic appearance of PEComa family tumors. Hematoxylin–eosin (H&E) staining of (A and B) typical angiomyolipoma (AML), (C and D) spindled AML, and (E and F) epithelioid AML. Black scale bar: 50 μm.