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Case Report

Malignant perivascular epithelioid cell tumor (PEComa) of cervix with *TFE3* gene rearrangement: a case report

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Abstract: In this study, we reported the first PEComa arising within the cervix with *TFE3* gene rearrangement and aggressive biological behavior. Morphologically, the tumor showed infiltrative growth into the surrounding parenchyma. The majority of tumor cells were arrayed in sheets, alveolar structures, or nests separated by delicate fibrovascular septa. There was marked intratumoral hemorrhage, necrosis, and stromal calcifications. The tumor cells had abundant clear cytoplasm, focally containing finely granular dark brown pigment, morphologically considered to be melanin. Immunohistochemically, the tumor cells demonstrated moderately (2+) or strongly (3+) positive staining for TFE3, HMB45, and Melan A but negative for CKpan, SMA, S100, PAX8, and PAX2. The presence of Ki-67 protein demonstrated a moderate proliferation rate, with a few Ki-67-positive nuclei. Using a recently developed *TFE3* split FISH assay, the presence of *TFE3* rearrangement was demonstrated. All these clinicopathologic features are suggestive of *TFE3*-rearranged PEComas of the cervix. Our results both expand the known characteristics of primary cervix PEComas and add to the data regarding *TFE3* rearrangement-associated PEComas.

Keywords: *TFE3*, translocation, rearrangement, perivascular epithelioid cell tumor, FISH, immunohistochemistry

Introduction

The perivascular epithelioid cell tumor (PEComa) family includes angiomyolipoma (AML) of the kidney and liver, clear cell sugar tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), lymphangiomyoma, cutaneous clear cell myomelanocytic tumor, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, sclerosing PEComas and a group of uncommon tumors (nonspecified PEComas) that arise in soft tissue, visceral organs, bone and skin [1-17].

Within the PEComa family, there is a strong association between AML and LAM and the tuberous sclerosis complex (TSC), an autosomal dominant genetic disease due to losses of *TSC1* (9q34) or *TSC2* (16p13.3) gene, which seems to have a role in the regulation of the rapamycin (mTOR) pathway [11, 14, 18]. The mTOR inhibitor sirolimus has demonstrated benefit in patients with metastatic PEComas [19].

Recently, a small subset of PEComas harboring gene fusions involving the *TFE3* gene has been recognized, suggesting a role for *TFE3* in the development of a subset of PEComa family tumors [20-25]. *TFE3* is one of four members of the microphthalmia-associated transcription factor (MITF) family, which includes *MITF*, *TFEB*, *TFEC* and *TFE3*. Several distinct tumors associated with the overexpression of this gene family, including melanoma, clear cell sarcoma, alveolar soft part sarcoma and translocation-associated renal cell carcinomas have been considered as a member of the microphthalmia-associated transcription factor family of tumors [26-31].

The overall clinicopathologic features of this distinctive subgroup of PEComas remains poorly understood because of their extreme rarity. It

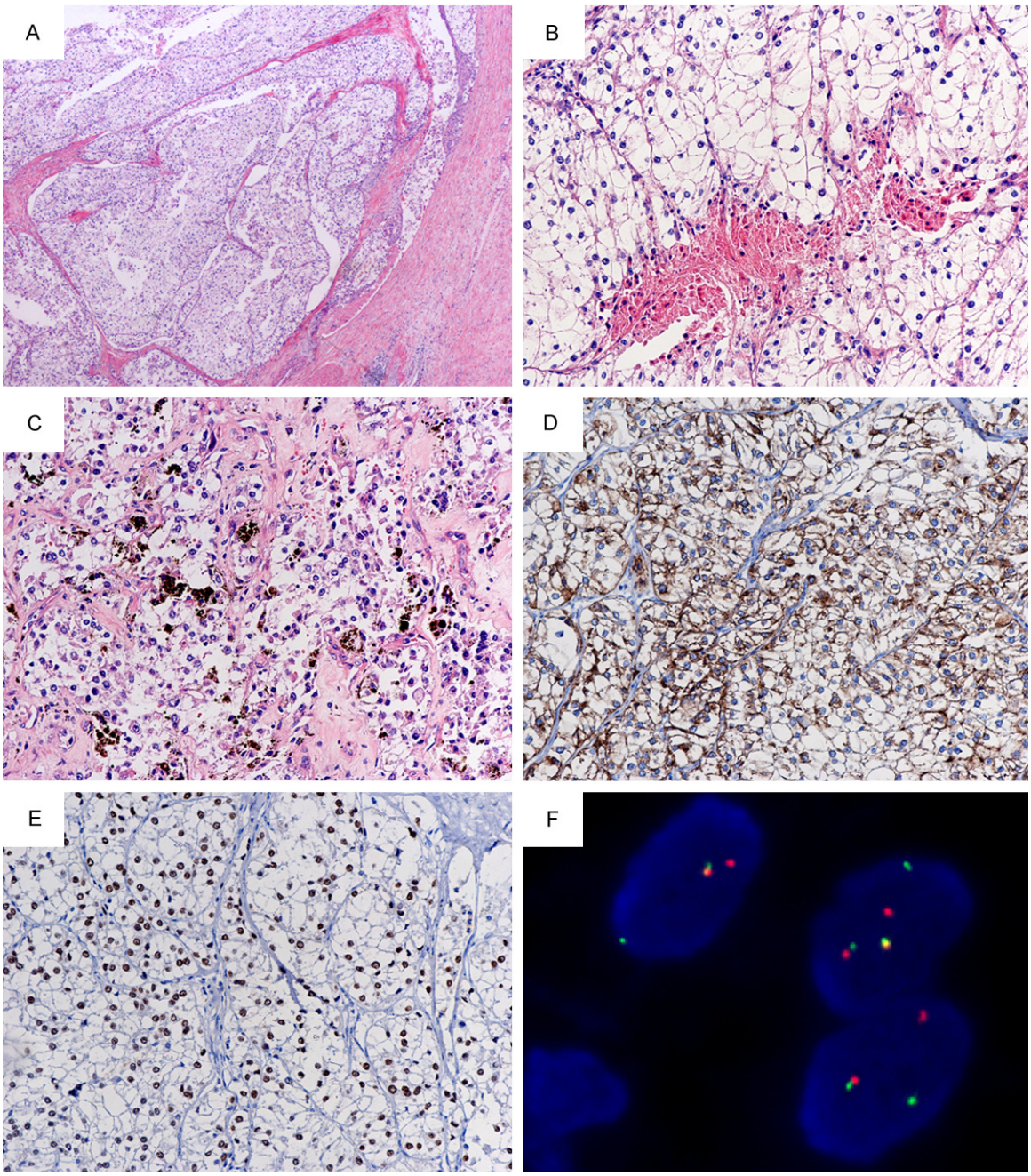

Figure 1. (A) The tumor showed infiltrative growth into the surrounding parenchyma. (B) The majority of tumor cells were arrayed in sheets, alveolar structures, or nests with necrosis separated by delicate fibrovascular septa. (C) The tumor cells had abundant clear cytoplasm, focally containing finely granular dark brown pigment, morphologically considered to be melanin, and had uniform round nuclei with small visible nucleoli. The tumor showed strong labeling for HMB45 (D) and TFE3 (E). (F) The *TFE3* split FISH assay showed an abnormal signal pattern consistent with both *TFE3* translocation and X chromosome polysomy.

was difficult to predict their clinical behavior, and easy to be misdiagnosed or neglected as common PEComas. Herein we reported the first PEComa arising within the cervix with *TFE3* gene rearrangement and aggressive biological behavior, and provided detailed clinical, histological, immunohistochemical, and molecular genetic features as well as follow-up data contributing to the number of cases reported in the literature.

Case report

Clinical history

A 34-year-old female with no significant past medical history was found abnormal vaginal bleeding 3 days. Vaginal ultrasound examination showed a 9 × 8 cm sized cervical mass. The mass resection was performed showing a 9.5 × 8.3 × 6 cm partly-encapsulated brownish-white tumor with multifocal hemorrhage areas. There was no familial history or clinical evidences of tuberous sclerosis. The tumor was found recurrence 2 months after operation and was partly resected. 5 months after the first operation, the patient was clinically suspicious for pelvic lymph nodes metastasis by imaging studies of abdomen, though she was alive.

Histopathological and immunohistochemical findings

Morphologically, the tumor showed infiltrative growth into the surrounding parenchyma. The majority of tumor cells were arrayed in sheets, alveolar structures, or nests separated by delicate fibrovascular septa. There was marked intratumoral hemorrhage, necrosis, and stromal calcifications. The tumor cells had abundant clear cytoplasm, focally containing finely granular dark brown pigment, morphologically considered to be melanin, and had uniform round nuclei with small visible nucleoli. Mitotic activity was occasionally observed (**Figure 1A-C**).

Immunoreaction was performed using the labelled streptavidin–biotin method and overnight incubation as previously described [32-33]. Immunohistochemically, the tumor cells demonstrated moderately (2+) or strongly (3+) positive staining for TFE3, HMB45, and Melan A but negative for CKpan, SMA, S100, PAX8, and PAX2. The presence of Ki-67 protein demonstrated a moderate proliferation rate, with a few Ki-67-positive nuclei (**Figure 1D**, **1E**).

TFE3 FISH analysis

As previous study, a split FISH ('break-apart') assay with probes centromeric (Green 5-fluorescein dUTP) and telomeric (Red 5-ROX dUTP) for *TFE3* was conducted to determine if a *TFE3* gene rearrangement was present [34]. The normal result is a combination (green and red) signal, whereas *TFE3* fusion results in a split signal. Signals were considered to be split when the green and red signals were separated by a distance >2 signal diameters. A positive result included 1 fused or closely approximated green-red signal pair (representing the uninvolved copy of the 6 chromosome) and an additional pair of split signals. A minimum of 100 tumor cell nuclei were examined under fluorescence microscopy at × 1000 magnification. Only nonoverlapping tumor nuclei were evaluated. Based on other commercially available break-apart FISH assays, a positive result was reported when >10% of the tumor nuclei showed the split-signal pattern [34]. The tumor showed an abnormal signal pattern consistent with both *TFE3* translocation and X chromosome polysomy locus in 45% of the cells (**Figure 1F**).

Discussion

Recently, it has been recognized that a subset of PEComas harbor translocations involving *TFE3*. These tumors are often associated with some distinctive pathologic features such as relatively young patient age, lack of tuberous sclerosis, epithelioid cytology with predominant nested-alveolar architecture, overlapping significantly with that of other *TFE3*-associated tumors (alveolar soft part sarcoma and Xp11.2 translocation renal cell carcinoma), no expression of smooth muscle actin or desmin and strong TFE3 immunoreactivity that contrast to those of PEComas without *TFE3* rearrangement. To our knowledge, only 9 molecularly confirmed cases have been described in the literature [20-25]. In this article, we report a case of malignant primary cervical PEComa with *TFE3* gene translocation detected by FISH. The case seems to fit this subset characterization and is the first reported primary cervical PEComa with molecular confirmation of this genetic alteration.

With respect to the cervix, morphology of epithelioid cytology with clear cytoplasm and predominant nested-alveolar architecture may suggest several soft tissue tumors, such as epithelioid leiomyosarcoma, metastatic malignant melanoma, clear cell sarcoma, and alveolar soft part sarcoma. Epithelioid leiomyosarcoma typically show immunoreactivity to antibodies against muscle marker SMA and lack immunoreactivity for melanocytic markers HMB45 and

Melan A. Positive melanocytic markers in combination with epithelioid cytology could be suggestive of a metastatic malignant melanoma and clear cell sarcoma. However, PEComas less frequently express S-100, and this serves as an important differentiating marker. Alveolar soft part sarcoma possesses *TFE3* rearrangement and characteristically shows positive immunostaining for TFE3 but does not show melanocytic differentiation.

TFE3 gene is one of four members of the microphthalmia-associated transcription factor (MITF) family, along with *TFEB*, *TFEC*, and *MiTF*, which located at chromosome Xp11.2. This site is also initially notable for its involvement in Xp11.2 translocations renal cell carcinomas and alveolar soft part sarcoma [26-28]. The true pathogenic contribution of the *TFE3* gene to PEComa tumors remains unclear, and it is difficult to predict the clinical behavior and obtain treatment experience of this subset, because of its rarity. In a previous study conducted by Agarni et al., as loss of heterozygosity for *TSC2* appears to be absent, it has been suggested that treatment modalities that have begun to be investigated for PEComas not otherwise specified, such as mTORC1 inhibitors, may not be useful in *TFE3*-rearranged PEComas [24, 35].

The criteria currently used for the malignant classification of PEComas was first proposed by Folpe et al. and includes tumor size, infiltrative growth, nuclear grade, cellularity, necrosis, vascular invasion, and mitotic rate as important prognostic factors [8]. The tumor in this study including infiltrative growth, size >5 cm, and necrosis met the criteria for malignant behavior and unfortunately pursued an aggressive course resulting in the tumor recurrence and pelvic lymph nodes metastasis. Our findings with an increasing number of *TFE3* rearrangement-associated PEComas demonstrating poor prognoses indicate that they also sometimes pursue an aggressive course [24]. Whether or not this malignant classification system should fit *TFE3* rearrangement-associated PEComas remains an open question, requiring further investigation of a larger number of cases.

In summary, we report on the first case of PEComa arising from the cervix associated with a *TFE3* gene break visible by FISH. The significance of *TFE3* gene rearrangement remains unclear, although this may represent a unique subset of PEComas with a distinctly biological course. These findings add to the data regarding *TFE3* rearrangement-associated PEComas.

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Disclosure of conflict of interest

None.

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References

[1] Chan JK, Tsang WY, Pau MY, Tang MC, Pang SW and Fletcher CD. Lymphangiomyomatosis and angiomyolipoma: closely related entities characterized by hamartomatous proliferation of HMB-45-positive smooth muscle. Histopathology 1993; 22: 445-455.

[2] Sullivan EJ. Lymphangioleiomyomatosis: a review. Chest 1998; 114: 1689-1703.

[3] Matsui K, Tatsuguchi A, Valencia J, Yu Z, Bechtle J, Beasley MB, Avila N, Travis WD, Moss J and Ferrans VJ. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. Hum Pathol 2000; 31: 1242-1248.

[4] Folpe AL, Goodman ZD, Ishak KG, Paulino AF, Taboada EM, Meehan SA and Weiss SW. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol 2000; 24: 1239-1246.

[5] Tazelaar HD, Batts KP and Srigley JR. Primary extrapulmonary sugar tumor (PEST): a report of four cases. Mod Pathol 2001; 14: 615-622.

[6] Vang R and Kempson RL. Perivascular epithelioid cell tumor ('PEComa') of the uterus: a subset of HMB-45-positive epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. Am J Surg Pathol 2002; 26: 1-13.

[7] Genevay M, Mc Kee T, Zimmer G, Cathomas G and Guillou L. Digestive PEComas: a solution when the diagnosis fails to "fit". Ann Diagn Pathol 2004; 8: 367-372.

[8] Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL and Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 2005; 29: 1558-1575.

[9] Mentzel T, Reisshauer S, Rutten A, Hantschke M, Soares de Almeida LM and Kutzner H. Cutaneous clear cell myomelanocytic tumour: a new member of the growing family of perivascular epithelioid cell tumours (PEComas). Clinicopathological and immunohistochemical analysis of seven cases. Histopathology 2005; 46: 498-504.

[10] Hornick JL and Fletcher CD. PEComa: what do we know so far? Histopathology 2006; 48: 75-82.

[11] Martignoni G, Pea M, Reghellin D, Zamboni G and Bonetti F. PEComas: the past, the present and the future. Virchows Arch 2008; 452: 119-132.

[12] Armah HB and Parwani AV. Perivascular epithelioid cell tumor. Arch Pathol Lab Med 2009; 133: 648-654.

[13] Sukov WR, Cheville JC, Amin MB, Gupta R and Folpe AL. Perivascular epithelioid cell tumor (PEComa) of the urinary bladder: report of 3 cases and review of the literature. Am J Surg Pathol 2009; 33: 304-308.

[14] Folpe AL and Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. Hum Pathol 2010; 41: 1-15.

[15] Yamashita K and Fletcher CD. PEComa presenting in bone: clinicopathologic analysis of 6 cases and literature review. Am J Surg Pathol 2010; 34: 1622-1629.

[16] Doyle LA, Hornick JL and Fletcher CD. PEComa of the gastrointestinal tract: clinicopathologic study of 35 cases with evaluation of prognostic parameters. Am J Surg Pathol 2013; 37: 1769-1782.

[17] Schoolmeester JK, Howitt BE, Hirsch MS, Dal Cin P, Quade BJ and Nucci MR. Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. Am J Surg Pathol 2014; 38: 176-188.

[18] Kenerson H, Folpe AL, Takayama TK and Yeung RS. Activation of the mTOR pathway in sporadic angiomyolipomas and other perivascular epithelioid cell neoplasms. Hum Pathol 2007; 38: 1361-1371.

[19] Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, Ligon AH, Antonescu CR, Ramaiya NH, Demetri GD, Kwiatkowski DJ and Maki RG. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 2010; 28: 835-840.

[20] Tanaka M, Kato K, Gomi K, Matsumoto M, Kudo H, Shinkai M, Ohama Y, Kigasawa H and Tanaka Y. Perivascular epithelioid cell tumor with SFPQ/PSF-TFE3 gene fusion in a patient with advanced neuroblastoma. Am J Surg Pathol 2009; 33: 1416-1420.

[21] Argani P, Aulmann S, Illei PB, Netto GJ, Ro J, Cho HY, Dogan S, Ladanyi M, Martignoni G, Goldblum JR and Weiss SW. A distinctive subset of PEComas harbors TFE3 gene fusions. Am J Surg Pathol 2010; 34: 1395-1406.

[22] Ohe C, Kuroda N, Hes O, Michal M, Vanecek T, Grossmann P, Tanaka Y, Tanaka M, Inui H, Komai Y, Matsuda T and Uemura Y. A renal epithelioid angiomyolipoma/perivascular epithelioid cell tumor with TFE3 gene break visualized by FISH. Med Mol Morphol 2012; 45: 234-237.

[23] Lee SE, Choi YL, Cho J, Kim T, Song SY and Sung CO. Ovarian perivascular epithelioid cell tumor not otherwise specified with transcription factor E3 gene rearrangement: a case report and review of the literature. Hum Pathol 2012; 43: 1126-1130.

[24] Williamson SR, Bunde PJ, Montironi R, Lopez-Beltran A, Zhang S, Wang M, Maclennan GT and Cheng L. Malignant perivascular epithelioid cell neoplasm (PEComa) of the urinary bladder with TFE3 gene rearrangement: clinicopathologic, immunohistochemical, and molecular features. Am J Surg Pathol 2013; 37: 1619-1626.

[25] Russell CM, Buethe DD, Dickinson S and Sexton WJ. Perivascular epithelioid cell tumor (PEComa) of the urinary bladder associated with Xp11 translocation. Ann Clin Lab Sci 2014; 44: 91-98.

[26] Davis IJ and Fisher DE. MiT transcription factor associated malignancies in man. Cell Cycle 2007; 6: 1724-1729.

[27] Medendorp K, van Groningen JJ, Schepens M, Vreede L, Thijssen J, Schoenmakers EF, van den Hurk WH, Geurts van Kessel A and Kuiper RP. Molecular mechanisms underlying the MiT translocation subgroup of renal cell carcinomas. Cytogenet Genome Res 2007; 118: 157-165.

[28] Haq R and Fisher DE. Biology and clinical relevance of the micropthalmia family of transcription factors in human cancer. J Clin Oncol 2011; 29: 3474-3482.

[29] Rao Q, Chen JY, Wang JD, Ma HH, Zhou HB, Lu ZF and Zhou XJ. Renal cell carcinoma in children and young adults: clinicopathological, immunohistochemical, and VHL gene analysis of 46 cases with follow-up. Int J Surg Pathol 2011; 19: 170-179.

[30] Rao Q, Zhang XM, Tu P, Xia QY, Shen Q, Zhou XJ and Shi QL. Renal cell carcinomas with t (6; 11) (p21; q12) presenting with tubulocystic re-

nal cell carcinoma-like features. Int J Clin Exp Pathol 2013; 6: 1452-1457.

[31] Rao Q, Liu B, Cheng L, Zhu Y, Shi QL, Wu B, Jiang SJ, Wang Y, Wang X, Yu B, Zhang RS, Ma HH, Lu ZF, Tu P, Wang JD and Zhou XJ. Renal Cell Carcinomas With t (6; 11) (p21; q12): A Clinicopathologic Study Emphasizing Unusual Morphology, Novel Alpha-TFEB Gene Fusion Point, Immunobiomarkers, and Ultrastructural Features, As Well As Detection of the Gene Fusion by Fluorescence In Situ Hybridization. Am J Surg Pathol 2012; 36: 1327-1338.

[32] Rao Q, Cheng L, Xia QY, Liu B, Li L, Shi QL, Shi SS, Yu B, Zhang RS, Ma HH, Lu ZF, Tu P and Zhou XJ. Cathepsin K expression in a wide spectrum of perivascular epithelioid cell neoplasms (PEComas): a clinicopathological study emphasizing extrarenal PEComas. Histopathology 2013; 62: 642-650.

[33] Rao Q, Wang Y, Xia QY, Shi SS, Shen Q, Tu P, Shi QL, Zhou XJ and Wu B. Cathepsin K in the immunohistochemical diagnosis of melanocytic lesions. Int J Clin Exp Pathol 2014; 7: 1132-1139.

[34] Rao Q, Williamson SR, Zhang S, Eble JN, Grignon DJ, Wang M, Zhou XJ, Huang W, Tan PH, Maclennan GT and Cheng L. TFE3 Break-apart FISH Has a Higher Sensitivity for Xp11.2 Translocation-associated Renal Cell Carcinoma Compared With TFE3 or Cathepsin K Immunohistochemical Staining Alone: Expanding the Morphologic Spectrum. Am J Surg Pathol 2013; 37: 804-815.

[35] Malinowska I, Kwiatkowski DJ, Weiss S, Martignoni G, Netto G and Argani P. Perivascular epithelioid cell tumors (PEComas) harboring TFE3 gene rearrangements lack the TSC2 alterations characteristic of conventional PEComas: further evidence for a biological distinction. Am J Surg Pathol 2012; 36: 783-784.