Annals of Diagnostic Pathology 19 (2015) 359–368

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Review Article

PEComa: morphology and genetics of a complex tumor family☆

Khin Thway, FRCPath *, Cyril Fisher, MD, DSc, FRCPath

Sarcoma Unit, Royal Marsden Hospital, London, UK

ARTICLE INFO

Keywords:
Perivascular epithelioid cell tumor
Angiomyolipoma
Clear cell myomelanocytic tumor
Lymphangioleiomyomatosis
TFE3
Tuberous sclerosis
Sirolimus

ABSTRACT

Perivascular epithelioid cell tumors, or PEComas, are mesenchymal neoplasms composed of histologically and immunohistochemically distinctive epithelioid or spindle cells, which are immunoreactive for both smooth muscle and melanocytic markers. The cells in PEComas are typically arranged around blood vessels and appear to form the vessel wall, often infiltrating the smooth muscle of small- to medium-sized vessels. Periluminal cells are usually epithelioid and the more peripheral cells are spindle shaped. The cells have small, round to oval nuclei, sometimes with focal nuclear atypia, and clear to eosinophilic cytoplasm, and no counterpart normal cell has been identified. The PEComa "family" now includes angiomyolipoma, pulmonary clear cell "sugar" tumor and lymphangioleiomyomatosis, primary extrapulmonary sugar tumor, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, and other tumors with similar features at various sites that are simply termed *PEComa*. Some PEComas occur in patients with tuberous sclerosis complex and share the genetic abnormalities. There is a behavioral spectrum from benign to frankly malignant, and histologic criteria have been proposed for assessing malignant potential. The differential diagnosis can include carcinomas, smooth muscle tumors, other clear cell neoplasms, and adipocytic tumors. PEComas constitute a genetically diverse group that includes neoplasms harboring *TFE3* gene rearrangements and those with *TSC2* mutations, indicating alternative tumorigenic pathways. Recent advances in therapy of malignant PEComas relate to increased knowledge of specific genetic changes and their effects on metabolic pathways that are susceptible to specific interventions. We review PEComas, emphasizing the diagnostic spectrum and recent immunohistochemical and genetic findings.

1. Introduction

PEComas are mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells (PECs), which are immunoreactive for both smooth muscle and melanocytic markers. The nature of these cells is, however, conjectural because no normal counterpart has been described. Bonetti et al [1] first noted an unusual cell type, which was immunoreactive with melanocytic markers and had an epithelioid appearance, clear-acidophilic cytoplasm and a perivascular distribution, in both angiomyolipoma (AML) and clear cell "sugar" tumor of the lung [2]. The PEComa "family" now additionally includes lymphangioleiomyomatosis (LAM), primary extrapulmonary sugar tumor [3], clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres (CCMMT) [4], abdominopelvic sarcoma of PECs [5], and other tumors with similar features at various sites that are simply termed *PEComa*. Some authors include renal capsular leiomyomas (capsulomas), but others consider them as monotypic spindle cell AML. There is an association between PEComas and tuberous sclerosis complex (TSC). The cells in PEComas are typically arranged around blood vessels and appear to form the vessel wall, often infiltrating the smooth muscle of small- to medium-sized vessels. Periluminal cells are usually epithelioid and the more peripheral cells are spindle shaped. Both cell types have small, centrally located round to oval nuclei with inconspicuous nucleoli, although there is sometimes focally marked nuclear atypia. The cytoplasm is clear or eosinophilic, and sometimes, there is clear cell change adjacent to a perinuclear eosinophilic zone. Rarely there is prominent melanin pigmentation. Fatty change can be seen, especially in the peripheral cells, which can mimic lipoblasts. The differential diagnosis can include carcinomas, smooth muscle tumors, and adipocytic neoplasms. In addition, a subset of PEComas is associated with *transcription factor E3* (*TFE3*) gene rearrangements, which appear to be mutually exclusive to those associated with tuberous sclerosis. More than 250 cases have now been reported [6], and there have been recent advances in therapy of malignant PEComas related to increased knowledge of specific genetic changes and their effects on metabolic pathways. This article reviews the morphologic, immunohistochemical, and genetic features of PEComas including assessment of malignant potential and likely response to therapy.

2. Angiomyolipoma

This accounts for less than 1% of renal tumors, but is the most common type of PEComa. Renal AML are found in up to 80% of patients

☆ Disclosures: The authors have no conflicts of interest or funding to disclose.

* Corresponding author at: Sarcoma Unit, The Royal Marsden NHS Foundation Trust, 203 Fulham Rd, London SW3 6JJ, UK. Tel.: +44 207 808 2631; fax: +44 207 808 2578.
E-mail address: khin.thway@rmh.nhs.uk (K. Thway).

http://dx.doi.org/10.1016/j.anndiagpath.2015.06.003
1092-9134/

known to have TSC [7], and the presence of multiple AML is diagnostic of TSC. However, approximately 90% of patients with AML do not have TSC. Renal AML have a mean age of diagnosis of 45 to 55 years for non-TSC patients and 25 to 35 years for those with TSC. Females outnumber males by 4:1 in surgical series, although the sex distribution is equal in radiologic studies, implying responsiveness to hormones. A small number of AML are described in other locations, notably the liver [8–16], but also in the spleen [17], heart [18], vagina [19,20], ovary [21], spermatic cord [22], palate [23], nose [24], mediastinum [25], retroperitoneum, and gastrointestinal tract. Apparently, benign monotypic epithelioid AML-like tumors have been described in the nasal cavity [26], liver [27], adrenal gland [28], and tibia [29].

Renal AML are expansile, noninfiltrative masses, which can grow during pregnancy and present with pain, hematuria, or symptoms of intratumoral hemorrhage. Renal microhamartomas might represent small AML. The tumors can arise in the cortex or medulla, or from capsular stromal proliferations, and are sharply demarcated from the adjacent kidney (Figs. 1A, B) but not encapsulated. Nodal involvement is not uncommon. Once regarded as a malformation, AML is now considered a clonal lesion (as initially demonstrated by nonrandom X-chromosome inactivation) [30,31] representing a neoplastic process involving all components.

Classic AML shows tortuous, thick-walled blood vessels, lipid-distended PECs resembling fat, irregularly arranged sheets and bundles of smooth muscle–like spindle cells and a clear eosinophilic component arranged around blood vessels (Fig. 1B). Both thick-walled vessels with walls composed of PEC and vessels with normal smooth muscle walls are present in AML, and lymphangiomyomatous areas can also be seen. Predominance of the myoid-appearing or lipid-distended PEC may be mistaken for smooth muscle or adipocytic tumors, respectively [32]. About 7% of cases of AML, especially in patients with TSC, can also show almost exclusively epithelioid morphology ("monotypic epithelioid AML"; Fig. 1C) [33–37]. Epithelioid AML can show striking cytologic atypia and multinucleation (Figs. 1C, D), and frankly malignant examples usually also have mitotic activity and focal necrosis. Epithelioid AML with clear cell change resembles extrapulmonary clear cell sugar tumor. Cystic [38,39] and intraglomerular [40] variants have been described. Renal cell carcinomas have been described in association with AML, both sporadically and in association with TSC. These are mostly clear cell carcinomas, but also include examples of chromophobe,

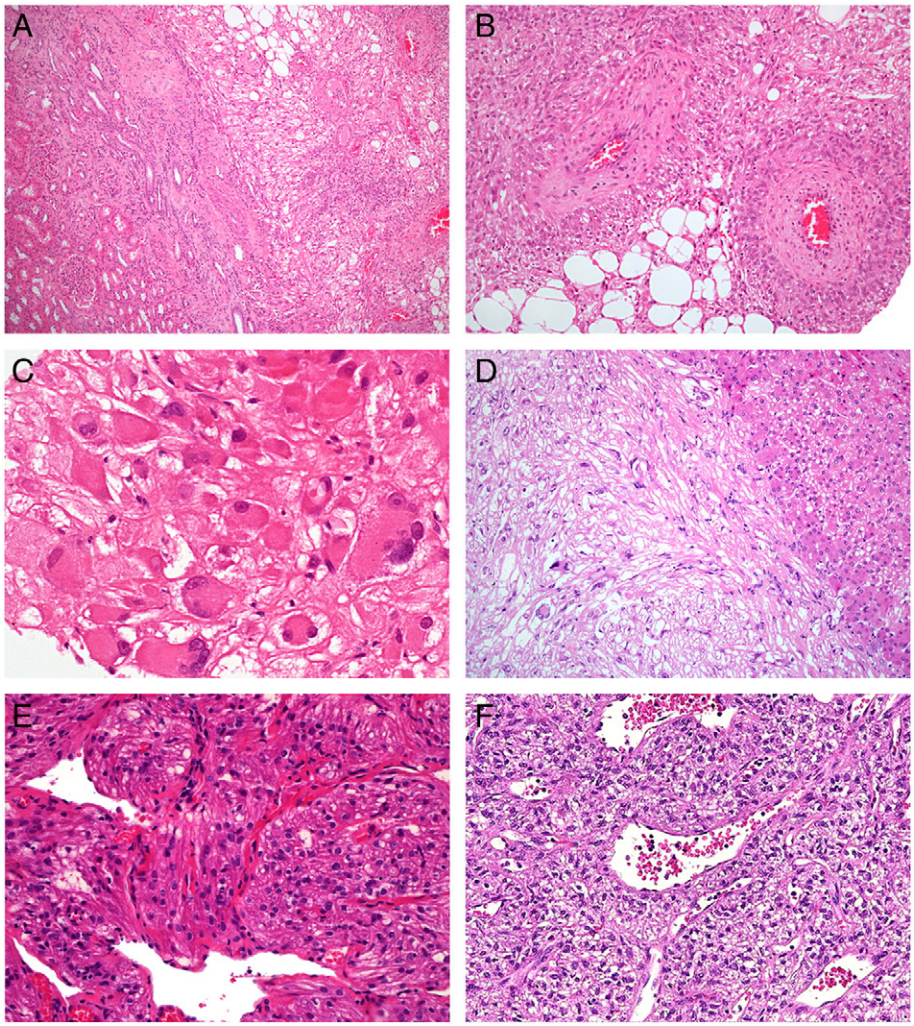

Fig. 1. (A) Angiomyolipoma. This renal AML is seen adjacent to and demarcated from the renal parenchyma. The lesion is unencapsulated, and comprises fatty and cellular components and thick-walled vessels. The cells show prominent vacuolation. (B) Angiomyolipoma. Classic AML shows tortuous, thick-walled blood vessels, with walls composed of PECs and vessels with normal smooth muscle walls. There are lipid-distended PECs resembling fat, irregularly arranged bundles of smooth muscle–like spindle cells and a clear to eosinophilic cell component arranged around blood vessels. (C) Epithelioid AML. About 7% of cases of AML, especially in patients with TSC, can also show almost exclusively epithelioid morphology ("monotypic epithelioid AML"). The cells contain eosinophilic or finely granular cytoplasm, which can resemble renal oncocytoma. Epithelioid AML can also show striking cytologic atypia and multinucleation, seen here. (D) AML of liver. Small numbers of AML are described in other locations, notably the liver. This example is composed of spindled and epithelioid cells, and cellular atypia is appreciable at low magnification. (E) Lymphangioleiomyomatosis. LAM is an abnormal proliferation of smooth muscle–like PEC around bronchial lymphatics, interlobular septa and pleura. Spindled and epithelioid cells form sheets and nodules in the lung. (F) Clear cell sugar tumor. The cells are uniform in size and polygonal and contain plentiful clear or granular eosinophilic cytoplasm with small nuclei and prominent cytoplasmic borders.