Perivascular Epithelioid Cell Tumor (PEComa) in the Genitourinary Tract
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Perivascular Epithelioid Cell

The Perivascular Epithelioid Cell (PEC) is a “novel” cell type showing morphological, immunoistochemical and ultrastructural distinctive features. It is characterized by an epithelioid appearance, a clear to granular cytoplasm, a central located round to oval nucleus with inconspicuous nucleoli, slight, if any, atypia and a perivascular distribution (1). PEC coexpresses myogenic and melanocytic markers. Immunoreactivity with HMB45, HMSA-1, Melan A/Mart1 and Microophthalmia Transcription Factor has been demonstrated in this cell, together with immunoreactivity for actin and, less consistently, desmin (1, 2, 3). Ultrastructurally, it exhibits microfilament bundles with electron-dense condensation, numerous mithocondria and membrane-bound dense granules (4, 5).

PEC is thought to be capable of dramatically modulating its morphology and immunophenotype. It can become spindle, with elongated nucleus and cytoplasm showing obvious muscular features or it can become vacuolized acquiring the characters of an adipocyte. The morphologic modulation of PEC is mirrored by its immunophenotypic modulation. Thus, a PEC with prevalent spindle morphology expresses muscle markers like actin more strongly than HMB45 whereas when it is purely epithelioid displays HMB45 immunoreactivity and focal, if any, actin positivity. The presence of progesterone receptors in the PEC with spindle morphology suggests a role of this hormone in its morpho-phenotypical modulation (1, 6). As today, the normal counterpart of PEC has not been identified.

In 1991, Pea et al. (7) first noted this unusual cell in both renal angiomyolipoma and clear cell sugar tumor of the lung. One year later Bonetti et al. (8) advanced the concept of a family of neoplasms composed by this distinctive cell and its association with Tuberous Sclerosis in a letter published in the American Journal Surgical Pathology. In 1996, Zamboni et al. (9) reported the first case of pancreatic clear cell sugar tumor and suggested to name PEComa those neoplasms composed by a pure proliferation of PECs.
Perivascular Epithelioid Cell Tumor (PEComas) of the genitourinary tract.

The World Health Organization defines PEComas as “mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells” (10). In the genitourinary tract they can occur in the kidney, in the bladder, in the prostate, in the uterus, in the ovary and in the vulva.

**KIDNEY**

PEComas of the kidney include classic angiomyolipoma, microscopic angiomyolipoma (so called microhamartoma), intraglomerular lesions, epithelioid angiomyolipoma, oncocytoma like-angiomyolipoma and lymphangiomyomatosis of the renal sinus.

*Classic angiomyolipoma* is the most common mesenchymal tumor of the kidney. The increasing diagnosis of asymptomatic angiomyolipoma seems to be due to the widespread use of ultrasonography performed to evaluate other conditions. Classic angiomyolipoma is characterized by the presence of a variable mixture of adipose tissue, spindle and epithelioid smooth muscle cells and abnormal thick-walled blood vessels (11, 12). It has been considered for a long time to be a hamartoma rather than a true neoplasm, but there is currently strong evidence arguing for its clonal nature (13, 14, 15). Angiomyolipoma can occur sporadically or in patients with Tuberous Sclerosis, a syndrome due to losses of TSCI (9q34) or TSC2 (16p13.3). Tuberous Sclerosis is a complex disease characterized by mental retardation, seizures, and cellular proliferations, including angiomyolipomas, subependymal giant cell tumors, cutaneous angiofibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis, and pulmonary multifocal micronodular hyperplasia. In patients with Tuberous Sclerosis, renal angiomyolipomas are found in both sexes, in the third and fourth decades of life, with a female predominance; they are usually asymptomatic, bilateral, small and multifocal. Sporadic angiomyolipomas occur in older patients, in the fourth to sixth decade of life, with a female predominance; they are single, unilateral and larger than those associated with Tuberous Sclerosis (12). Classic angiomyolipoma contains more than one cell type, but occasionally adipocytes (lipoma-like angiomyolipoma) or spindle smooth muscle cells (leiomyoma-like
angiomyolipoma) predominate in a particular lesion. Classic angiomyolipoma have a benign outcome. Multifocality and regional lymph node involvement can occur and this is considered to represent a multifocal growth pattern rather than metastasis (16, 17). Three cases of sarcoma developing in sporadic angiomyolipoma have been reported, although a similar event has not been described in Tuberous Sclerosis patients (18, 19, 20).

Angiomyolipoma frequently shows loss of heterozigosity of variable portions of the TSC2 gene locus in both sporadic and Tuberous Sclerosis-associated tumours. The TSC1 gene occasionally shows loss of heterozigosity (21, 22).

Microscopic angiomyolipomas (so called microhamartomas) are small nodules often present in the kidney bearing angiomyolipomas. They are not homogeneous in appearance and display all the varied morphologic features of angiomyolipoma less the thick-wall blood vessels (1, 23).

Intraglomerular lesions with features overlapping with those of angiomyolipoma have been reported in patients with and without Tuberous Sclerosis and in the TSC2/PKD1 contiguous gene syndrome, a disease with a deletion disrupting both TSC2 and PKD1 (autosomal dominant polycystic disease gene) (24).

Epithelioid angiomyolipoma is a recently described variant of angiomyolipoma. This tumor is composed of purely epithelioid cells with melanogenesis markers immunoreactivity arranged in sheets and characterized by the absence of both adipocytes and abnormal blood vessels. The cytoplasm of the neoplastic cells in these tumors varies from faintly eosinophilic to clear. These cells can display considerable nuclear atypia and can resemble ganglion cells. Epithelioid angiomyolipoma closely resembling high-grade or sarcomatoid renal cell carcinomas is responsible for the occasionally misdiagnosed angiomyolipoma. This tumor can recur locally, metastasise and cause death. On the basis of histology alone it is not possible to predict malignant behaviour in these neoplasms and further data are needed to better define it. However, at the present time, all epithelioid angiomyolipomas should be closely followed clinically. Epitheliod angiomyolipoma has been described in patient with or without evidence of Tuberous Sclerosis and in the TSC2/PKD1 contiguous gene syndrome.

Loss of heterozigosity of TSC2 have been reported in one case of sporadic epithelioid angiomyolipoma (24, 25, 26, 27).
Tumors composed of a homogeneous population of HMB45 positive polygonal cells with deeply eosinophilic cytoplasm have been identified in patients with and without Tuberous Sclerosis and are called **oncocytoma-like angiomyolipoma**. Recognition of this variant is significant because oncocytomas in the same kidney with angiomyolipomas have been reported repeatedly, and in patients with Tuberous Sclerosis, oncocytomas seem to occur more frequently than in general population (28).

Lymphangiomyomatosis is a rare and progressive disease that affects the lungs of women usually during their reproductive years. In the lung, it consists of an interstitial proliferation of HMB45 positive smooth muscle cells which can vary from small spindle-shaped cells to large epithelioid cells (5). This lesion has also been reported in extrapulmonary sites including mediastinal and retroperitoneal lymph-nodes and soft tissue of the mesentery and the renal sinus. **Lymphangiomyomatosis of the renal sinus** is a plaque-like mass in the wall of the renal pelvis. All three cases reported to date also had renal angiomyolipomas, but in only two out of the three cases careful post-mortem examination of the lungs revealed pulmonary lymphangiomyomatosis (24, 29).

**BLADDER AND PROSTATE**

In 2003, Pan et al have reported two PEComas of the genitourinary tract occurring in patients without Tuberous Sclerosis (30, 31). One of them measured 8 cm in diameter and involved the prostate and the left seminale vesicule of a 46-year-old male whereas the other of 4 cm arose from the muscularis propria of the urinary bladder in a 33-year-old-woman. Both tumors were composed of a variable percentage of epithelioid and spindle cells with clear to granular cytoplasm arranged in nests separated by a vascular stroma. The neoplastic cells were positive for HMB45, but not for epithelial markers, vimentin and S100 protein. The prostatic tumor showed a low mitotic activity, coagulative necrosis and a malignant behaviour whereas the neoplasm of the bladder, lacking these histologic findings, behaved in a benign fashion. The major differential diagnosis of PEComa, especially around the anatomic site of prostate and urinary bladder, should include smooth muscle tumors (leiomyoma and leiomyosarcoma), malignant melanoma, clear cell sarcoma of the soft part, paraganglioma, postoperative spindle cell nodule/inflammatory myofibroblastic proliferation and clear cell or sarcomatoid carcinomas.
PEC neoplasms can rarely involve the female genital tract. The first case reported by Pea et al (32) was a polypoid neoplasm involving the endometrium, which showed morphological features closely related to the clear cell “sugar”tumor of the lung. Vang and Kempson (33) described eight cases of uterine perivascular epithelioid cell tumor (“PEComa”). Patients ranged in age from 40 to 75 years (mean 54 years). They distinguished a morphologic spectrum of neoplasms varying from tumors with a tongue-like growth pattern composed of sheets of HMB45-positive clear epithelioid cells, which they called group A, to circumscribed tumors composed of hyalinized stroma and neoplastic cells focally positive for HMB45 and extensively immunoreactive for actin and desmin, which they referred to as group B. A tumor with a strong and diffuse HMB45 expression morphologically corresponding to an epithelioid angiomyolipoma has been reported in the ovary (34). Finally, one case described as primary extrapulmonary sugar tumor of the vulva has been reported by Tazelaar et al. (35). Lesions considered to be uterine involvement of lymphangiomyomatosis are usually asymptomatic and some of them correspond to an incidental finding in patients bearing stigmata of Tuberous Sclerosis. The PEComas of the uterus have usually shown benign behaviour, but thirteen tumors, two of them associated with Tuberous Sclerosis, were aggressive (36). Recently Folpe et al reported 26 cases of PEComas of soft tissue and gynecologic origin (vagina, cervix and uterus) proposing criteria for the classification of these tumors as “benign”, “of uncertain malignant potential”, and “malignant” (37). In this study they observed a significant association between tumor size >5 cm., infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity > 1/50 HPF and subsequent aggressive clinical behaviour.

REFERENCES


