Inflammatory Myofibroblastic Tumor of the Bladder. How Does it Relate to Other Lesions With this Name?

Elizabeth Montgomery, MD
Department of Pathology
Johns Hopkins Hospital
Weinberg 2242, 401 N. Broadway
Baltimore, MD 21231
emontgom@jhmi.edu

Background:
Pulmonary lesions called “inflammatory pseudotumors” were known for many years and were regarded as part of a spectrum of lesions called “plasma cell granulomas” (1-5). Various terms were applied: inflammatory pseudotumor, plasma cell granuloma, plasma cell pseudotumor, xanthomatous pseudotumor, pseudosarcomatous myofibroblastic proliferation, and inflammatory myofibrohistiocytic proliferation (6). Subsequently, similar tumors were described in the abdomen and other soft tissue sites (6, 7). As we have learned more about a wide spectrum of lesions in this family of myofibroblastic proliferations in a host of anatomic sites (8-16), questions concerning their etiology and biologic potential remain. Advances in understanding of the molecular biology of these tumors, launched by the discovery of a “hot spot” at 2p23 flanking the \textit{ALK} gene by Griffin et al (17), have provided some insights, but other questions remain unanswered. Following the report by Griffin and her colleagues (17) of these alterations in soft tissue lesions, other investigators confirmed similar alterations in other sites, including the lung, the classic site (18). Immunohistochemistry for the protein product confirmed protein expression in subsets of these lesions in a range of anatomic sites (15, 16, 19-26), although Cessna et al noted that this staining was not wholly specific (25). These tumors have been linked, on the one hand, to nodular fasciitis (27), and, on the other hand, to cells of the accessory immune system that have been variously called fibroblastic reticulum cells, myoid cells, and dictyocytes (28).

Inflammatory Myofibroblastic Tumor and Inflammatory Fibrosarcoma of Soft Tissues

Although these lesions were originally described as separate entities, they are now recognized as ends of a spectrum of tumors unified by a common molecular profile (6, 23, 29-32). They are grouped together by the WHO (33, 34). Gene fusions involving anaplastic lymphoma kinase (ALK) at chromosome 2p23 have been described (19, 32, 35, 36). By immunohistochemistry, ALK has been detected in about 60% of cases, a finding that can sometimes be exploited for diagnosis (19). In a subset of cases, ALK C-terminal kinase domain is fused with tropomyosin N-terminal coiled-coil domain and other cases have shown fusion of ALK with the clathrin heavy chain (32).

Inflammatory fibrosarcoma

This is most common in childhood with a mean age of 8 years (range 2 mos to 74 years). As described in the AFIP series (7), this tumor arises within the abdomen, involving mesentery, omentum and retroperitoneum (over 80% of cases), with occasional cases in the mediastinum, abdominal wall and liver. Sometimes there are associated systemic
symptoms. The tumor can be solitary or multinodular (30%) and up to 20 cm in diameter. The tumors are composed of myofibroblasts and fibroblasts in fascicles or whorls, and also histiocytoid cells. Pleomorphism is moderate, but mitoses are infrequently seen. There is a variable but often marked inflammatory infiltrate, predominantly plasmacytic but with some lymphocytes, and occasionally neutrophils or eosinophils as well. Fibrosis and calcification can be seen in the stroma. Immunostaining is positive for SMA and some examples express cytokeratin especially where there is submesothelial extension. The tumors invade adjacent viscera; 37% recurred and 3 cases (11%) metastasized. A quarter of the patients died of disease.

The differential diagnosis from inflammatory myofibroblastic tumor is subjective as these conditions are ends of a spectrum (one case was included in both the original papers describing these two conditions). Essentially, it depends on the presence of pleomorphism in cases designated as “fibrosarcoma”.

**Inflammatory myofibroblastic tumor**

Also known as inflammatory pseudotumor, this entity was first well-described in the lungs and later became recognized in extra-pulmonary locations(6). Recent cytogenetic and molecular evidence in both inflammatory myofibroblastic tumor and inflammatory fibrosarcoma supports a clonal origin, implying that this process is neoplastic. It is found in soft tissue, in omentum and retroperitoneum and involving viscera. IMT has been reported in patients between 3 months and 46 years, but mostly in childhood (mean age 9 years) with a slight male predominance, and some cases are associated with systemic symptoms. A small number recur, especially when multinodular. They form firm white infiltrative masses, and histologically there are three patterns: (1) fasciitis-like, with vascular, myxoid and inflamed stroma, including plasma cells; (2) fascicular MFH or leiomyosarcoma like spindle cell areas with inflammation; (3) sclerosed desmoid-like areas with calcification.

**Bladder**

A spindle cell lesion in the bladder reminiscent of nodular fasciitis was described in 1980 as “reactive pseudosarcomatous response” (37) and subsequently, this process was found elsewhere in the genitourinary tract (38-40). Identical lesions were subsequently encountered in patients who had undergone prior instrumentation, and these were called “post-operative spindle cell nodules”(41, 42). Other terms have included inflammatory pseudotumor, nodular fasciitis, pseudomalignant spindle cell proliferation, pseudosarcomatous myofibroblastic proliferation, pseudosarcomatous myofibroblastic tumor, and inflammatory myofibroblastic tumor (22). The unifying feature of these lesions is their proclivity to mimic both sarcomas (43)and spindled carcinomas(44), the latter compounded by their expression of various keratins(20, 39, 40, 43-47). It had been assumed that, since these tumors have been benign in small follow-up studies(44), that they were unrelated to lesions with similar names in other anatomic sites and, thus, more akin to nodular fasciitis. However, they differed by nodular fasciitis in their capacity to infiltrate deeply into the detrusor muscle.

The recent identification of ALK alterations in bladder lesions (20, 22, 48) suggests that, despite the lesions’ frequent similarity to nodular fasciitis, they are probably neoplastic. It has also led to re-evaluation of their relationship to similar proliferation in the soft tissues. Since those in the bladder often appear fasciitis-like with
a loose myxoinflammatory appearance, whereas those in other sites can be fascicular, sclerosed, or laden with plasma cells and foam cells, bladder lesions had been regarded simply as counterparts of nodular fasciitis.  

In our own material, bladder lesions are highly likely (about 70%) to be ALK reactive on immunohistochemistry and to harbor ALK alterations on FISH studies (about 75%), certainly supporting that most are not simply reactive processes. Most cases display nuclear p53 on immunohistochemistry as well as keratin reactivity.  

Most patients with bladder lesions are adults (mean age in 40s with a range from childhood to elderly patients) males (about 3:1) who present with hematuria. There is a history of instrumentation in about 20% of patients. Some lesions are quite cellular with mitoses and necrosis, and bladder wall invasion is not uncommon.  

The vast majority of patients have an indolent course (although 10-25% experience recurrences), but we have recently encountered 2 cases in which biopsies showing bladder IMT preceded (1 and 2m, respectively) biopsies showing sarcomatoid carcinoma associated with high grade invasive urothelial carcinoma accompanied with separate fragments of bladder IMT; even on re-review the bladder IMT in these 2 cases were morphologically indistinguishable from other cases of bladder IMT, with FISH demonstrating ALK alterations in the bladder IMT areas in 1 of the 2 cases. These 2 patients both died of their carcinomas. A further case displayed overtly sarcomatous features and displayed ALK alterations by FISH and the patient subsequently died of this malignant neoplasm. As such, currently, when we encounter atypical features in these lesions, we now advise caution in our reports and do not render an unequivocally benign interpretation. When lesions appear typical and fasciitis-like, we note that most are benign but mention recurrences and even association with malignant neoplasms as remote possibilities.  

The question remains as to whether bladder IMT is the same lesion as lesions called IMT in the rest of the body. Bladder lesions are far more likely to express keratin than those in other sites and are probably less likely to recur and certainly less likely to metastasize [although metastases are rare in soft tissue examples and remain the subject of debate]. They do share molecular alterations and should for the present at least be regarded as a subtype of the general family of IMT. Conservative management and follow-up is advised for most cases.  

The most important components of the differential diagnosis are sarcomatoid urothelial carcinoma, leiomyosarcoma, and rhabdomyosarcoma. It is well known that some sarcomatoid urothelial carcinomas exhibit myxoid features mimicking IMT. IMT often expresses cytokeratin, and sarcomatoid urothelial carcinoma sometimes shows weak or focal immunoreactivity for cytokeratin, making the differential diagnosis even more difficult. Finding marked cytologic atypia, atypical mitotic figures, and nonmyxoid areas with marked increased cellularity usually allows for a diagnosis of sarcomatoid carcinoma, but the most useful feature is the identification of an in situ or invasive “typical” epithelial component.  

Some leiomyosarcomas of the bladder display myxoid zones and can also express cytokeratin. The lack of a delicate vascular network and interspersed inflammatory cells and red blood cells, which are usually observed in IMT, and the presence of marked cytologic atypia and atypical mitoses in leiomyosarcomas may be helpful in the differential diagnosis. Leiomyosarcomas and leiomyomas lack ALK-1. In the pediatric setting, embryonal rhabdomyosarcoma is the key contender in the differential diagnosis,
an entity readily separated by application of an immunohistochemical panel that includes MyoD1 or myogenin.

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Perivascular Epithelioid Cell Tumor (PEComa) in the Genitourinary Tract
Guido Martignoni, Maurizio Pea, Giuseppe Zamboni, Franco Bonetti.
Anatomia Patologica, Università di Verona, Verona, Italy.

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 Microphthalmia 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 TSC1 (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. Epithelioid 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 vescicle 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.
UTERUS, OVARY AND VULVA

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


