Inflammatory Myofibroblastic Tumor in Female Genital Tract

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• Context.—Inflammatory myofibroblastic tumor is a mesenchymal neoplasm of low malignant potential. It was first described in lung, but is known to occur in many extrapulmonary sites including female genital organs, most commonly the uterus. It has a high recurrence rate and a low risk for metastasis. A more recently described aggressive variant, epithelioid myofibroblastic sarcoma with a predilection for the abdominal cavity of males, has also been recently reported to occur in the ovary. This tumor is composed of spindled and epithelioid myofibroblasts in a variably myxoid stroma and commonly shows a fascicular growth pattern with positive staining for desmin, smooth muscle actin, and CD10, which may mimic a smooth muscle or endometrial stromal neoplasm. In the female genital tract it has the potential for being misdiagnosed as a leiomyoma, endometrial stromal tumor, or as a myxoid leiomyosarcoma, resulting in undertreatment or overtreatment. It harbors rearrangements in the ALK gene, resulting in abnormal expression of ALK protein. Immunostaining for ALK is a helpful diagnostic tool.

• Objective.—To provide a brief review of clinical, histologic, immunohistochemical, and molecular features of inflammatory myofibroblastic tumor with emphasis on possible diagnostic pitfalls in the female genital tract.

• Data Sources.—Review of pertinent literature on inflammatory myofibroblastic tumor occurring in the female genital tract and personal experience of the authors.

• Conclusions.—Inflammatory myofibroblastic tumor in the female genital tract can mimic other more common benign and malignant tumors like leiomyoma, leiomyosarcoma, and endometrial stromal sarcoma. Familiarity with clinical and histologic features and use of ALK immunostaining can be critical for correct diagnosis.

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Inflammatory myofibroblastic tumor (IMT) is a mesenchymal neoplasm of myofibroblastic differentiation. It is classified as a tumor of intermediate malignant potential under the World Health Organization classification of tumors of soft tissue and bone with a recurrence rate of 25% and metastasis in less than 2% of cases. Originally described as inflammatory pseudotumor in the lung, it has been referred to with several other names, including plasma cell granuloma, xanthomatous pseudotumor, and pseudosarcomatous myofibroblastic proliferation, and has been reported in many extrapulmonary sites in the body, including mesentery, omentum, retroperitoneum, head/neck, pelvic cavity, urogenital tract, and extremities. It was initially regarded as a reactive lesion based on benign follow-up in small case series; however, its potential to recur and occasionally metastasize was later established in larger studies. More recently, discovery of cytogenetic aberrations involving chromosome band 2p23 resulting in ALK (anaplastic lymphoma kinase) gene rearrangement in approximately half of the IMTs has established the neoplastic origin of this entity. Up to 50% of IMTs have been shown to express ALK protein by immunohistochemistry with reactivity ranging from 36% to 71% in various large studies including up to 73 cases. Genomic rearrangement and fusion involving other receptor tyrosine kinases including ROS1, RET, NTRK3, and PDGFRB have been found in IMTs that are negative for ALK rearrangement. Currently, IMT is considered a distinct neoplastic lesion with characteristic clinical, histomorphologic, and cytogenetic features within the broad family of inflammatory pseudotumors that also includes various postinfectious/reparative lesions. A histologically distinctive and clinically aggressive variant of IMT with epithelioid morphology and characteristic nuclear membrane or perinuclear staining with ALK immunohistochemistry has recently been described as epithelioid inflammatory myofibroblastic sarcoma (EIMS).

Gynecologic IMTs are relatively uncommon although they may be underrecognized, as their morphologic features overlap with other mesenchymal tumors more commonly seen in the female genital tract, namely, smooth muscle and endometrial stromal cell neoplasms. Patients with recurrent or metastatic IMT can benefit from ALK inhibitor–based targeted therapy, therefore, accurate diagnosis of these lesions is important. In this review, we discuss the clinical, morphologic, and molecular features of IMTs occurring in the female genital tract with an emphasis on their
distinction from other mesenchymal tumors in the female genital tract.

**CLINICAL FEATURES**

In the female genital tract IMT has been reported in the uterus, cervix, ovaries, fallopian tubes, broad ligament, para- adenial soft tissue, pelvic cavity, and placenta. Within the gynecologic tract, the most common site for IMT reported in the literature so far is the uterine corpus followed by the cervix. Age at presentation has ranged from 6 years to 73 years. The most common clinical presentation is with mass-associated symptoms, that is, abdominal discomfort, abdominal distension, pelvic pain and pressure, stress incontinence, and dyspareunia. Menstrual irregularities (menorrhagia, abnormal uterine bleeding, irregular menstrual cycles) are also common presenting complaints. Constitutional symptoms of fatigue, fever, malaise, anorexia, and weight loss have also been recorded at the time of presentation. Some patients may have mild leukocytosis, thrombocytosis, elevated sedimentation rate, and elevated C-reactive protein levels. Elevated serum levels of interleukin 6, and its production by neoplastic cells of IMT, have been implicated in the constitutional symptoms and elevated sedimentation rate, elevated C-reactive protein levels, thrombocytosis, and leukocytosis, among others. Serum tumor marker (CA 125) may be within normal range or elevated in some cases, especially if the tumor presents as a disseminated disease in the abdominopelvic cavity. Some patients may be asymptomatic and their tumor is discovered incidentally. There seems to be an association between uterine IMT and pregnancy as in a recent retrospective study in which 2 of 19 uterine leiomyomata (10.53%) removed during pregnancy turned out to be uterine IMT as compared to only 3 of 1728 leiomyomas (0.17%) removed from nonpregnant women. Ovarian IMTs are rare and reported in pediatric age groups. They are usually large and present with mass-associated symptoms as well as constitutional symptoms mimicking sepsis. There are anecdotal reports of young female patients presenting with disseminated disease in the form of multiple masses in the abdominopelvic cavity, resembling disseminated leiomyomatosis or carcinomatosis clinically. There are 3 reports of incidental IMTs in placenta, which ranged in size from 1.5 to 3 cm. All 3 were attached to decidua and have been speculated to be uterine IMTs secondarily involving the placenta.

**HISTOPATHOLOGY**

Approximately half of uterine IMTs are submucosal polypoid masses sometimes pedunculated. The other half may be seen as discrete intramural, transmural, or subserosal masses or may involve both myometrium and endometrium. Their borders may range from being smooth to irregular, pushing or infiltrative. Extrauterine extension of tumor may be seen in some patients at the time of initial presentation. In published literature, the size of uterine IMTs has ranged from 1.5 to 20 cm. The macroscopic appearance of uterine IMTs has been described as tan pink or white with interspersed yellow areas and firm to fleshy to soft and gelatinous/mucinous/myxoid consistency. Areas of cystic change, foci of hemorrhage, and necrosis may be seen. Some uterine IMTs may have typical gross appearance of leiomyoma with tan white whorled surfaces and occasional areas of myxoid change. In pelvic cavity and para-adnexal spaces also, IMT nodules are described as polypoid, well circumscribed, but deeply invading the adjacent soft tissue and firm to friable in consistency. Figure 1, A and B, shows 2 examples of uterine IMTs from our files. Microscopically, IMTs in the female genital tract are similar to IMTs seen elsewhere in the body. Three basic histologic patterns have been described that are seen in various combinations within the same tumor.
myxoid pattern is most common. It is hypocellular and is characterized by loosely arranged plump to spindle cells in an edematous or myxoid stroma with an irregular network of delicate blood vessels and a prominent mixed inflammatory infiltrate (Figure 2, A). This pattern resembles nodular fasciitis or may have a granulation tissue–like appearance. This pattern may also show areas with dense or storiform growth of spindle cells with interspersed myxoid stroma (Figure 2, B) or scattered areas of acellular myxoid pools. The second pattern is compact and consists of hypercellular regions of fascicular or storiform arrangement of spindle cells with elongated plump nuclei resembling smooth muscle cells. Inflammatory cells, mostly plasma cells, are seen either as small aggregates or more uniformly dispersed within the compact pattern (Figure 2, C). Occasionally, the cells in the compact pattern may resemble endometrial stroma (Figure 2, D). The third pattern is of areas of hyalinized, sparsely cellular collagen. Scattered plasma cells or lymphocytes may be seen entrapped in dense eosinophilic collagen (Figure 2, E). Nuclear atypia ranges from mild (bland spindle cells with thin elongated nuclei; Figure 3, A) to moderate (spindle cells with elongated plump vesicular nuclei; Figure 3, B) to severe (with large, rounded, vesicular nuclei and conspicuous nucleoli; Figure 3, C). Most nuclear atypia is seen in the myxoid pattern. Ganglion-like cells with eosinophilic cytoplasm and eccentric nuclei with nucleoli are often seen interspersed in myxoid and compact patterns (Figure 3, D). Mitotic activity is low in most cases. It may be brisk occasionally, but atypical mitotic figures are rarely seen.2,3,14 Necrosis is seen rarely. Inflammatory infiltrate is commonly lymphoplasmacytic but often includes neutrophils, foamy histiocytes, eosinophils, and Touton giant cells. Lymphoid aggregates with germinal centers and clusters of plasma cells may be noted. Most tumors show thin-walled elongated blood vessels. Scattered thick-walled blood vessels may also be noted. Chicken wire–like vasculature (Figure 4, A) and scattered staghorn vessels may also be seen (Figure 4, B). Some tumors may show foci of angiolymphatic invasion.2,3,9,12,14

In placental IMTs and the IMTs removed from pregnant patients, the spindle cells show decidual change.14,29,36 The interface of tumor with myometrium may be pushing, focally irregular, or frankly infiltrative with nodular/tongue-like invasive pattern seen in endometrial stromal sarcoma. Infiltration may also be seen as a jagged sawtooth appearance or percolation of tumor cells into the myometrium. Necrosis and vascular invasion are rare.2,3,9,12,14

MOLECULAR FEATURES AND IMMUNOHISTOCHEMISTRY

IMTs commonly harbor chromosomal rearrangements resulting in fusions of the 3′ kinase-containing portion of ALK to the 5′ portion of a constitutively expressed gene, resulting in activation of the kinase domain and abnormal expression of ALK protein.31 ALK expression by immunohistochemistry (IHC) and/or ALK rearrangement by fluorescence in situ hybridization (FISH) are diagnostic of IMT. Multiple ALK fusion partner genes have been recognized including TPM3, SEC31, IGFBP5, TIMP3, THBS1, and DES.9,13 Recently, Haimes et al32 have shown that uterine IMTs are rich in ALK fusions with novel ALK fusion partners IGFBP5 and THBS1. IMTs lacking ALK genetic rearrangements/fusions have been shown to have genomic rearrangements/fusions involving other receptor tyrosine kinases including NTRK3, PDGFRB, RET, and ROS1.7,31

Expression of ALK protein by IHC is indicative of ALK rearrangement.5,32 One of the 13 cases of uterine IMT reported by Bennett et al34 was negative for ALK by IHC; however, it showed ALK rearrangement with DES-ALK fusion by FISH. The authors thought that the use of a more sensitive ALK antibody clone could have potentially resulted in positive staining for ALK. Although they used mouse monoclonal antibody clone 5A4 (Leica Biosystems, Buffalo Grove, Illinois), which has been validated to be highly sensitive and specific for presence of ALK rearrangements,9,32 rabbit monoclonal antibody for ALK (clone DSF3, Ventana Medical Systems Inc, Tucson, Arizona) is reported to be more sensitive and specific for ALK rearrangements than Leica 5A4.33 In uterine IMTs the rate of ALK positivity by immunohistochemistry ranges from 88% to 100% in different published case series.2,12-14 although it should be noted that not all ALK antibodies, dilutions, and retrieval conditions may be equally sensitive and specific, and optimization and validation of the ALK antibody in individual laboratories before clinical use is recommended.4 Leica 5A4 clone for ALK antibody has been validated at high concentration (1:10) by Pickett et al2 to be highly sensitive and specific for presence of ALK rearrangements. Ventana clone DSF3 is reported to be more sensitive and specific for ALK rearrangements than Leica 5A4 by others.32,33

From their experience of false-negative ALK immunostaining in 1 of their 13 cases, Bennett et al14 recommend testing with other modalities including a different antibody clone, FISH, next-generation sequencing, or immunostaining for non-ALK rearrangements (ROS1) in cases with compelling histologic features of IMT but negative ALK immunohistochemistry.

In extraterine IMTs, patterns of immunostaining have been correlated with specific gene fusions depending on the location of the fusion partner such as nuclear membrane staining with RANBP2-ALK fusion, since RANBP2 is a nuclear pore protein.5 In uterine IMTs all cases have shown cytoplasmic staining pattern (Figure 5, A). ALK expression by myofibroblasts is seen in fascicular zones as well as in myxoid areas. A recently reported case of ovarian epithelioid inflammatory myofibroblastic sarcoma (an aggressive variant of IMT) with RANBP2-ALK fusion showed ringlike nuclear membrane expression of ALK by immunohistochemistry.34

Haimes et al33 describe a case with histologic features of IMT, a parancellular coarse granular staining pattern with ALK immunohistochemistry, and negative FISH result. This case was initially diagnosed as leiomymoma because coarse parancellular ALK staining was considered negative in light of the negative FISH result for ALK rearrangement. In this case the FISH result was found to be falsely negative because this case harbored an IGFBP5-ALK fusion that was detected by RNA sequencing, and the diagnosis was changed to IMT. They concluded that the FISH result was falsely negative because IGFBP5 and ALK both reside on chromosome 2; the spatial separation between the 5′ and 3′ signals was subtle and not appreciated on FISH. Correlating FISH findings with the ALK immunohistochemistry and the histologic features is recommended, as FISH results can be falsely negative when the fusion partners are on the same chromosome, and ALK immunostaining patterns can vary depending on the localization of fusion partners.
Figure 2. Uterine inflammatory myofibroblastic tumor. A, Myxoid hypocellular area with loosely arranged spindle cells and mixed inflammatory infiltrate. B, Myxoid area with dense growth of spindle cells and scattered inflammatory cells. C, Compact area with dense fascicular architecture resembling leiomyoma. D, Compact area with sheetlike arrangement resembling endometrial stroma. E, Hyalinized area with abundant collagen deposition (hematoxylin-eosin, original magnification ×10 [A through E]).
Figure 3. Uterine inflammatory myofibroblastic tumor. A, Mild nuclear atypia with slender nuclei. B, Moderate nuclear atypia with plump, vesicular nuclei. C, Large, rounded, vesicular nuclei with nucleoli. D, Ganglion-like cells with eccentric nuclei and eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×40 [A through D]).

Figure 4. Uterine inflammatory myofibroblastic tumor. A, Chicken wire–like vascular pattern. B, Staghorn blood vessels (hematoxylin-eosin, original magnification ×10 [A and B]).
Other immunostains that are expressed in IMTs are markers of myofibroblastic differentiation, namely, smooth muscle actin, desmin (Figure 5, B), and calponin. Focal cytokeratin staining may also be seen. CD10 can show strong and diffuse staining in IMT (Figure 5, C). Uterine IMTs are reported to be positive for estrogen and progesterone receptors as well.\(^2,6,12,14\) Immunostaining with these markers makes it challenging to distinguish IMTs from more commonly occurring smooth muscle and endometrial stromal tumors in the female genital tract. p53 overexpression is seen in up to 80% of cases of IMT; however, Ki-67 index is generally low.

**PROGNOSIS**

IMTs in general are indolent tumors with 25% recurrence rate and distant metastasis in approximately 2% of cases.\(^1\) Attempts to identify features predicting behavior of IMT in individual cases have been inconclusive. Strong associations between tumor size, nuclear atypia, cellularity, mitotic activity, presence of necrosis, and tumor behavior have not been found in studies of IMTs from various anatomic sites. ALK expression has been associated with a very low risk of metastasis as compared to ALK-negative IMTs; however, ALK reactivity does not correlate with recurrence. Presence of nuclear atypia and ganglion-like cells was suggested to be indicative of aggressive behavior; however, changes were also seen in more than half of clinically benign IMTs.\(^9\) In their series of 13 cases of uterine IMTs, Bennett et al\(^14\) associated tumor size of more than 10.5 cm, presence of severe nuclear atypia, greater than 18 mitoses per 10 high-power fields, and lymphovascular invasion with malignant behavior.

A subset of IMTs with epithelioid morphology, positive ALK staining in a distinctive ringlike nuclear membrane pattern, and \(\text{RANB2-ALK}\) fusion by FISH represents an aggressive tumor that is termed *epithelioid inflammatory myofibroblastic sarcoma*. In contrast to classic IMT, patients with EIMS develop frequent recurrences and have an overall median survival of 11 months. This entity has a predilection for the abdominal cavity and is more commonly seen in males. A single case report of its occurrence as an ovarian mass in a 15-year-old has been published recently.\(^24\)

**DIAGNOSTIC PITFALLS IN THE FEMALE GENITAL TRACT**

Distinguishing IMTs in the female genital tract from benign and malignant smooth muscle cell tumors can be difficult, as compact zones of IMT with dense areas of bland spindle cells with elongated plump nuclei, arranged in fascicles, resemble smooth muscle cell tumors. Immunostaining with smooth muscle actin and desmin further contributes to their similarity with smooth muscle tumors. IMTs have been misdiagnosed as leiomyoma, smooth muscle tumor of uncertain malignant potential (STUMP), or myxoid leiomyosarcoma depending on the presence of predominantly fascicular areas, nuclear atypia, tumor necrosis, mitotic figures, and infiltrative borders.\(^9,10,32\) A
helpful feature for distinguishing IMTs from smooth muscle tumors is finding myxoid areas with lymphoplasmacytic infiltrate and nodular fasciitis or tissue culture–like appearance seen in IMT. Benign smooth muscle tumors may show myxoid change in a degenerative setting, and myxoid leiomyosarcomas show extensive myxoid areas but they lack inflammatory infiltrate and nodular fasciitis–like appearance in their myxoid regions. Atypical nuclei of IMT are pale, fusiform, with evenly dispersed chromatin and prominent nucleoli, while nuclei of myxoid leiomyosarcoma are typically hyperchromatic. A large proportion of uterine IMTs are submucosal; therefore, it is prudent to consider the possibility of IMT when dealing with a submucosal mass especially if it shows myxoid areas or inflammatory infiltrate.

Pregnancy also seems to have an association with IMT; therefore, consideration of a diagnosis of IMT for uterine tumors removed during pregnancy is reasonable. Diagnosis of IMT must be considered before diagnosing benign metastasizing leiomyoma or carcinosarcoma in young women presenting with multiple nodules in pelvic or abdominal cavity. Immunostaining with ALK can be diagnostic for IMT, as both benign and malignant smooth muscle tumors are ALK negative.

IMTs may show areas of uniform cells in diffuse sheets, resembling endometrial stroma (Figure 2, D). Strong CD10 immunostaining and tonguelike infiltrative pattern seen in IMTs can lead to a misdiagnosis of endometrial stromal tumor or endometrial stromal sarcoma. Myxoid change is rare in endometrial stromal tumors and it lacks the lymphoplasmacytic infiltrate characteristic of IMT. Spiral arterioles commonly seen in endometrial stromal tumors are not seen in IMT. Endometrial stromal tumors are also negative for ALK expression. Occasionally, extragastrointestinal stromal tumor (E-GIST) involving pelvic organs may be in the differential diagnosis, as myxoid areas have been reported in GIST; however, presence of lymphoplasmacytic infiltrate is not seen in GIST. Immunohistochemistry can be useful, as GISTs are negative for ALK expression, and C-kit (CD117) expression has not been reported in IMT.

**SUMMARY**

Inflammatory myofibroblastic tumor is a neoplasm of uncertain malignant potential with approximately one-fourth of cases experiencing recurrence and low rate of metastasis. It infrequently occurs in the female gynecologic tract; however, it may be underrecognized, as it shows morphologic and immunohistochemical overlap with benign and malignant smooth muscle tumors and endometrial stromal tumors, which are much more frequently diagnosed in the female genital tract. Accurate diagnosis is important as patients with IMT should be followed up for the possibility of recurrence, and patients with recurrent or metastatic IMT can benefit from ALK inhibitor–based targeted therapy with crizotinib. Knowledge of histomorphologic features of IMT, a low threshold for ALK immunostaining of tumors with histomorphologic features suggestive of IMT, and awareness of different patterns of ALK immunostaining can help with accurate diagnosis.

**References**


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