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Mullerian Mesenchymal Neoplasm with Endometrial Stromal and Smooth Muscle Differentiation: A Case Report and Review of Literature

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Abstract

This is a case report of a 60-year-old female with a history of post-menopausal bleeding. She came to Karmanos Cancer Institute for a second opinion. In August 2018, she had her first endometrial biopsy which was reported as cellular spindle cell proliferation compatible with cellular leiomyoma. Subsequent scans revealed an enlarged uterus, multiple adenopathy in the pelvis and the thorax, and multiple right-sided pulmonary nodules. Then she underwent a left-para-aortic lymph node biopsy in November 2018, and a biopsy of her mediastinal lymph node in January 2019, both of which were reported as benign spindle cell neoplasms consistent with metastasizing leiomyoma. Subsequently, in March 2019, she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy that was reported as low-grade endometrial stromal sarcoma with smooth muscle differentiation. FISH analysis for known anomalies in endometrial stromal sarcoma was inconclusive. After a thorough evaluation of all her pathology slides, we concluded that her neoplasm had similar morphology and immuno-profile in the uterus, bilateral ovary, pelvic sidewall, and metastatic lymph nodes. Post-surgery, she is being managed with chemotherapy as a case of low-grade endometrial stromal sarcoma and she has not had a recurrence of her neoplasm in one and a half years. In our opinion, the presence of this extensive mixed neoplasm, although favoring low-grade-endometrial stromal sarcoma, most likely represents a complex tumor of the Mullerian duct system. A possibility of such neoplasms arising from a common mesenchymal stem cell in the Mullerian duct system is yet to be investigated.

Keywords: Endometrial Stromal Sarcoma, Mullerian Mesenchymal Neoplasm, Endometrial Stromal Sarcoma with Smooth Muscle Differentiation, Metastasizing Leiomyoma, Mesenchymal Neoplasm of Mullerian Duct System

Case Presentation

Patient is a 60-year-old female with history of post-menopausal bleeding. She came for a consult at Karmanos Cancer Institute. In August 2018 she underwent endometrial biopsy that was reported as cellular spindle cell proliferation most compatible with cellular leiomyoma. Subsequent CT scans revealed enlarged uterus, and multiple adenopathy involving pelvic, para-aortic and mediastinal lymph nodes. In November 2018, she underwent a biopsy of the left para-aortic lymph node. The biopsy of the left para-aortic lymph node revealed a low-grade spindle cell neoplasm showing cells arranged in fascicles and few interspersed small blood vessels. The cells showed immunoreactivity with smooth muscle actin (SMA), desmin, estrogen receptor (ER); and no reactivity with HMB-45, PAX-8, and ALK. The diagnosis was favored as a benign metastasizing leiomyoma. In January 2019, she underwent a mediastinoscopy and biopsy that showed low-grade spindle cell neoplasm.

In March 2019, she underwent hysterectomy and bilateral salpingo-oophorectomy. Grossly, it was difficult to identify the ovaries from the adnexal tissue. The endometrial cavity was distorted by multiple nodules measuring from 0.2 cm to 8.5 cm.

Sections from the myometrium, and bilateral ovaries shows multiple well circumscribed nodules with variable cellularity. Patchy areas showed spindle cells with abundant eosinophilic cytoplasm, arranged in long fascicles and affiliated with cleft like spaces consistent with smooth muscle differentiation [figure3,5]. Hyaline necrosis is seen in areas of smooth muscle differentiation [figure 4,6]. Patchy areas show highly cellular, haphazardly

arranged spindle cells with low mitotic activity consistent with endometrial stromal sarcoma [Figure 3]. Multiple areas of lympho-vascular invasion were seen. No coagulative necrosis was seen. Both components were diffusely positive for CD10, SMA, progesterone receptor (PR), and desmin (variable intensity) and focally positive for estrogen receptor (ER). The foci of smooth muscle differentiation showed more immunoreactivity to desmin than the foci of endometrial stromal differentiation.

Florescence in-situ hybridization (FISH) analysis performed at Mayo clinic was negative for JAZF1, PHF-1, and YWHAE gene rearrangement. Since the tumor could not be established as a single well-established entity, it was signed out as low-grade endometrial stromal sarcoma (LGESS) with smooth muscle differentiation.

Follow-up:

The patient is currently on phase I protocol 2018-156 that utilizes ALKS 4230 administered subcutaneously every 7 days in combination with pembrolizumab given every 21 days. She is stable to receive Pembrolizumab and ALKS 4230 subcutaneously for cycle 11. There is no increase in the size of mediastinal and pulmonary nodules from the start of this treatment.

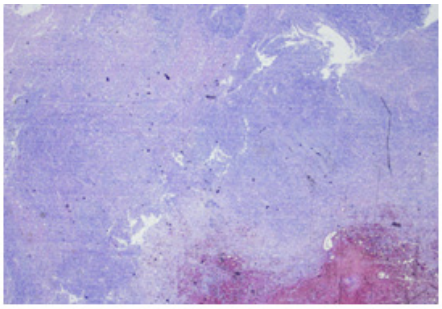


Figure 1: Section from the right pelvic sidewall mass

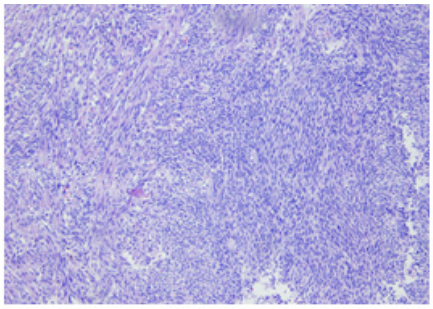


Figure 2: Section from the right pelvic sidewall mass

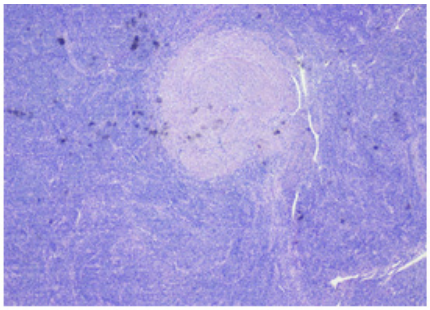


Figure 3: Section from nodular area in the uterus

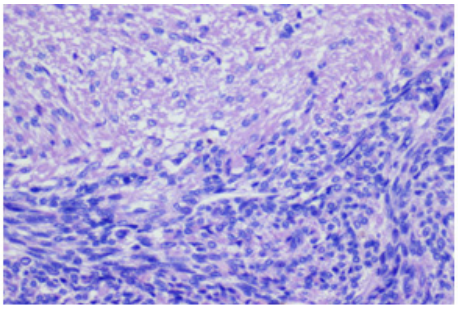


Figure 4: Section from nodular area in the uterus

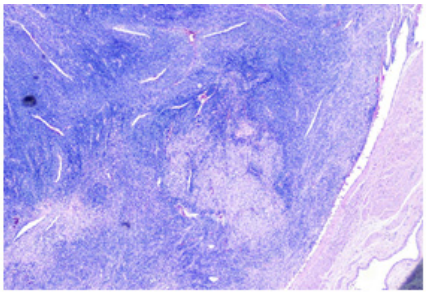


Figure 5: Section from the right adnexal mass

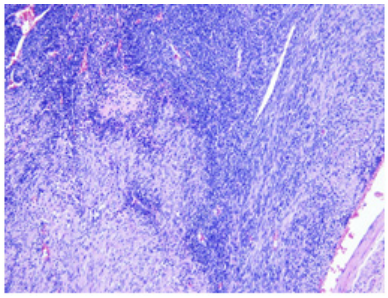


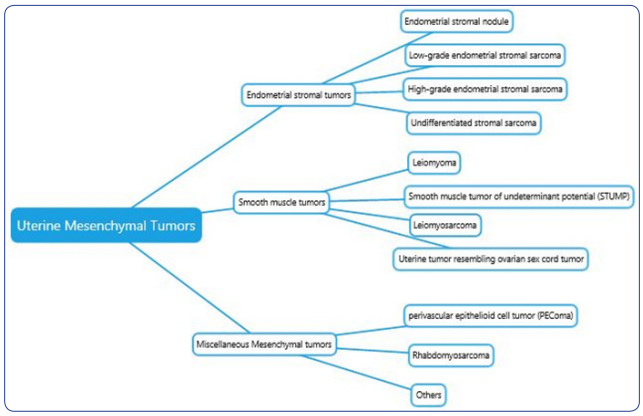
Figure 6: Section from the right adnexal mass

Literature review

Uterine mesenchymal tumors can be endometrial stromal tumors, smooth muscle tumors, or miscellaneous sarcomas that include rhabdomyosarcoma and Peri-vascular epithelial stromal tumor [1]. Ovarian primary mesenchymal tumors can be stromal sarcomas and leiomyosarcomas [2,3]. The primary ovarian stromal sarcomas are classified into low-grade and high-grade endometrioid stromal sarcoma and share similar histologic features to endometrial stromal sarcomas.

Endometrial stromal tumors are a relatively rare entity classified into Endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma (HGESS), and undifferentiated uterine sarcoma [4]. The benign end of the spectrum is endometrial stromal nodule, that forms a well circumscribed nodule and resembles the proliferative phase endometrial stroma. It can have finger-like projections measuring a maximum of 3 mm. The cells are relatively bland looking, will minimal mitotic activity, and do not have lympho-vascular invasion. They show similar immunoreactivity and molecular

alterations as in low -grade endometrial stromal sarcoma.



Histologically, low-grade endometrial stromal sarcomas resemble stromal cells of proliferative phase endometrium. They have an infiltrative growth pattern into the myometrium with/without lympho-vascular invasion [5]. Tumor cells grow in sheets and typically show minimal cytologic atypia and low mitotic activity. Hyaline plaques, foamy histiocytes, hemorrhage, and necrosis can be also seen. Smooth muscle differentiation can be often seen as nodules with central hyalinization and radiating collagen bands that at the periphery encircle rounded cells (starburst pattern) that merge with smooth muscle. They can also show a fibro myxoid change, or/and sex cord- like differentiation. Skeletal muscle differentiation, rhabdoid, epithelioid, clear cell change, focal bizarre nuclei (for sarcoma), adipocyte differentiation, pseudopapillary appearance and multinucleated giant cells are rarely seen [6]. JAZF1, PHF-1, and YWHAE gene rearrangement is often seen associated with low-grade endometrial stromal sarcoma [7].

High grade endometrial stromal sarcomas show variable morphology based on the molecular characterization. They show an invasive and destructive pattern of spindle cells, with high mitotic count and necrosis [8]. YWHAE-FAM22, ZC3H7B-BCOR, and BCOR ITD are a few known molecular sub-types of high grade endometrial stromal sarcoma [9].

Undifferentiated stromal sarcoma lacks any resemblance to proliferative phase endometrial stroma and shows pseudopapillary/glandular architecture with mitosis >10 per 10 high power field (hpf), and necrosis [10]. However, undifferentiated uterine sarcoma may be classified as high-grade endometrial stromal sarcoma if seen intermixed by low-grade component.

Smooth muscle neoplasm of the uterus consists of leiomyoma, smooth muscle tumor of indeterminant significant, and leiomyosarcomas. Leiomyomas are frequently encountered in anatomic pathology. They are benign smooth muscle tumors and have varied morphologic patterns. Although they are benign, a few cases of metastatic leiomyomas outside the uterus have been identified. Leiomyomas are well circumscribed, spindle shaped cells arranged in fascicles.

A few noteworthy variants of leiomyomas are cellular leiomyomas, leiomyomas with bizarre nuclei, mitotically active leiomyoma, fumarate hydratase (FH) gene deficient leiomyomas (associated with Renal cell carcinoma), and intravenous leiomyomatosis. Cellular leiomyomas are, as the name suggests, highly cellular and mimic endometrial stromal sarcomas. However, the presence of thick walled medium to large sized vessels within the cellular region favor a diagnosis of cellular leiomyoma [11]. IVL is characterized by the presence of benign smooth muscle within vascular spaces outside the confines of a leiomyoma, free floating within the lumen or adherent to the vessel wall. The cells are usually bland with rare mitoses. A worm-like growths of smooth muscle are observed grossly [12].

FH gene deficient leiomyoma is characterized by multiple leiomyomas that frequently have increased cellularity, Eosinophilic globules that can be mistaken for hyalinized type necrosis, multinucleated and atypical nuclei with prominent red to orange nucleoli [13].

Smooth muscle tumor of uncertain malignant potential (STUMP) is a smooth muscle tumor with features that preclude an unequivocal diagnosis of leiomyosarcoma, but that do not fulfill the criteria for leiomyoma. The diagnosis of smooth muscle tumor of uncertain malignant potential is based on coagulative cell necrosis, moderate to severe cytologic atypia and mitotic figures. Furthermore, they cannot be classified as benign and malignant [14]. Case of Stump with metastatic pulmonary nodules have been reported [15].

Leiomyosarcomas can be sub-classified as spindle cell type, epithelioid type, and myxoid type. They show a high-grade cytology with high mitotic count, tumor cell necrosis, and per-vascular distribution of the tumor [16]. They are immunoreactive for desmin, h-caldesmon, SMA; and can also express immunoreactivity for CD10, and EMA, and may express CD117 and DOG-1. Strong and diffuse p16 immunoreaction, especially when accompanied by p53 strong positivity favors leiomyosarcoma. Leiomyosarcomas have both complex numerical and structural chromosomal aberrations. Frequent losses of 10q and 13q as well as occasional gain of 17p and losses of 2p and 16q, TP53, RB1, α-thalassemia/mental retardation syndrome X-linked (ATRX) and mediator complex subunit 12 (MED12) have been reported [17].

Uterine tumor resembling ovarian sex cord tumor resembles ovarian sex cord tumors, without a component of recognizable endometrial stroma. They are well circumscribed but may have a pseudo-infiltrative appearance due to incorporated smooth-muscle bundles. The tumor cells are usually immunoreactive for cytokeratin and WT-1, frequently for smooth muscle actin or desmin and less commonly for sex cord markers. The tumors do not have the JAZF1- SUZ12 fusion that characterizes endometrial stromal tumors, indicating that they are unlikely to be of endometrial stromal derivation [18].

Perivascular epithelioid cell tumor (PEComa) is a mesenchymal tumor, typically showing epithelioid cells that exhibit a clear to eosinophilic, granular cytoplasm demonstrating melanocytic and smooth muscle differentiation. It is thought to be derived from the perivascular epithelioid cell. Tumor cells express HMB-45, Melan- A, and D-240 [19].

Discussion

Presented in this case are unusual findings suggestive of both low grade endometrial stromal sarcoma and smooth muscle tumor in the uterus, ovary, pelvic side wall, and in the para-aortic lymph node. The low grade endometrial stromal sarcoma differentiation is composed of bland, spindle shaped tumor cells that are smaller in size with high N/C ratio and hyperchromatic nuclei. The areas of smooth muscle differentiation show patchy hyalinized (infarct type) necrosis. No cytologic atypia was noted within the smooth

muscle component, and the mitotic index was calculated around 2 per 10 HPF. The two histological differentiations can be appreciated blending with each other. However, sections from the uterus had a predominance of the endometrial stromal differentiation, whereas sections from the ovary, pelvic side wall [figure 1,2], and the para-aortic lymph node showed a predominance of smooth muscle differentiation. If present independently, the above-mentioned features of endometrial stromal differentiation favor a diagnosis of low-grade endometrial stromal sarcoma, and the smooth muscle component favors a diagnosis of cellular leiomyoma.

But the existence of the two differentiation in varying proportions at different locations lead to significant inter-observer disagreement on the diagnosis of this entity. The diagnosis was even more challenging due to the lack of support of molecular alteration in JAZF1, PHF1, and YWHAE. However, the presence or absence of these mutations does not rule in or rule out endometrial stromal sarcoma, as they can be false positives and false negatives in around 50 % of cases [20]. Complex structural aberrations, like loss of 10q, 2p, 16q, and 13q reported in leiomyosarcomas, were not tested.

The differential diagnosis included low-grade endometrial stromal sarcoma with smooth muscle differentiation, mixed endometrial stromal and smooth muscle sarcoma, uterine leiomyosarcoma, cellular leiomyoma, and Mullerian mesenchymal neoplasm with both endometrial stromal and smooth muscle differentiation.

It is often challenging to distinguish cellular leiomyoma from endometrial stromal tumor due to significant overlapping histology and IHC. In this Case, the two components expressed distinct immunoreactivity to Desmin. The presence of vascular invasion with at least focal myometrial infiltrative growth pattern argues against a benign process such as a benign metastasizing leiomyom although, intravenous leiomyomatosis and LGESS can have prominent intravascular growth.

Alternate diagnosis included endometrial stromal sarcoma with smooth muscle differentiation. However, sections from the ovary, pelvic side wall, and lymph node showed a predominance of smooth muscle differentiation with prominent vasculature. A diagnosis of cellular leiomyoma cannot be made when multiple areas show features suggestive of low grade-endometrial stromal sarcoma with haphazard arranged fascicles without intervening blood vessels.

There are two possibilities which are the least likely. One possibility was that of FH deficient leiomyoma as hyalinized necrosis can be easily confused with the eosinophilic globules. However, sections did not show alveolar pattern edema, chain like distribution of tumor cells, cherry red macro nucleoli, and staghorn shaped blood vessels that can be seen in fumarate hydratase deficient leiomyoma. The last possibility was presence of an endometrial stromal sarcoma and cellular leiomyoma; but the smooth muscle component and the endometrial stromal component blended with each other. High grade endometrial stromal sarcoma and leiomyosarcoma were not favored due to lack of significant mitosis and cytologic atypia.

In our opinion, the presence of this mixed neoplasm in the ovary, uterus, pelvic side wall, and para-aortic lymph nodes, although favoring low-grade-endometrial stromal sarcoma, most likely represents a complex tumor of the Mullerian duct system. Due to the presence of tumor in both the ovary and the uterus, it is designated as a Mullerian neoplasm. This unusual mesenchymal tumor exhibiting such varying morphology in both the ovary and the uterus has not been reported. This case represents an unexplored area of mesenchymal neoplasm and the entire Mullerian duct system. A possibility of such neoplasms arising from a common mesenchymal stem cell in the Mullerian system is yet to be investigated.

Conflict of Interest

The authors have no conflict of financial interest.

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