



Educational Case

Educational Case: Metastatic endometrial stromal sarcoma presenting as bone pain: a diagnostic approach to uterine mesenchymal tumors



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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme>.¹

Keywords: Pathology competencies, Organ system pathology, Female reproductive- uterus, Uterine neoplasia, Uterine mesenchymal tumors, Endometrial stromal sarcoma, Cytopathology, Genetic basis of endometrial stromal sarcoma

Primary objective

Objective FU1.1: Clinical features of uterine neoplasms. Compare and contrast common benign and malignant uterine neoplasms, including important clinicopathological features related to treatment and prognosis.

Competency 2: Organ system pathology; Topic: Female reproductive—uterus (FU); Learning goal 1: Uterine neoplasia

Secondary objectives

Objective N1.1: Genetic mechanisms of neoplasia. Discuss and provide examples of molecular genetic mechanisms that underlie cancers, including germline mutations (including point mutations, deletions, amplifications, and translocations) and epigenetic changes.

Competency 1: Disease mechanisms and processes; Topic: Neoplasia (N); Learning goal 1: Genetic basis of neoplasia

Objective N3.1: Morphologic features of neoplasia. Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease mechanisms and processes; Topic: Neoplasia (N); Learning goal 3: Characteristics of neoplasia.

Objective CYP1.4: Use of cytology for staging of neoplasms. Describe how cytologic specimens can add valuable information for tumor staging.

Competency 3: Diagnostic medicine and therapeutic pathology; Topic: Cytopathology (CYP); Learning goal 1: Cytologic diagnosis.

Patient presentation

A 55-year-old woman presents to her primary care physician with progressive upper and lower back pain for several months. She describes the pain as dull, achy, and unchanged by physical activity. She does not report injury to her back or any wounds on her back. Non-steroidal drugs initially alleviated the pain, but they no longer provide pain relief. She has a history of uterine malignancy that was initially diagnosed eight years prior, and for which she underwent hysterectomy, adjuvant hormonal therapy and chemotherapy. However, despite treatment, she has developed metastases to the pelvic lymph nodes and to the lung.

Diagnostic findings, Part 1

The patient's vital signs are within normal limits. Palpation of the bony prominences of the thoracic spine elicits tenderness, particularly at the level of the T10 vertebra. The patient also notes that palpation of the right iliac crest is painful. There is no pain with palpation of the paraspinal muscles or ligaments. The skin overlying these areas shows no erythema or induration. No focal deficits are noted on neurological examination of these areas.

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Questions/discussion points, Part 1

Based on the clinical presentation, what is the most likely differential diagnosis for this patient?

During physical examination, it is important to attempt to localize the painful tissue compartment. This patient had tenderness with palpation of the bony prominences of the thoracic spine and iliac crest, thus making it more likely that the pathology lies in the bone or in the immediate surrounding soft tissue.

Given the patient's history of metastatic uterine malignancy, bony metastases of her known malignancy would be an obvious consideration. However, it is crucial to investigate and exclude other possibilities, including inflammatory conditions, trauma, and other tumors, both benign and malignant. Inflammatory conditions like osteomyelitis usually result from penetrating injury of the overlying skin and resulting subcutaneous infection that spreads to involve the bone.² However, this patient is denying any wounds over the hip or spine and there is no evidence of current or recent skin infection on physical exam. Trauma-induced fractures in this patient seem less likely since she does not report injury to the painful areas.

For neoplastic conditions, primary bone tumors must be considered, as well as tumors metastasizing to bone. Primary bone tumors that could be considered in this patient include both benign tumors such as fibrous dysplasia, and malignant tumors, like chondrosarcoma and osteosarcoma. However, the fact that the patient's pain is multifocal (thoracic spine and iliac crest) makes a metastatic tumor more likely than a primary bone tumor.^{3,4} Multifocal primary bone tumors can rarely be seen in a syndromic context, such as McCune Albright syndrome or metachondromatosis, but this is far rarer than metastatic bone disease, and syndromic conditions tend to manifest at an earlier age.^{3,4} Lastly, chondrosarcoma and osteosarcoma would be more likely to form large masses involving long bones, rather than small tumors at two distant locations.^{3,4}

Although it would be very unfortunate for the patient to have a new malignancy that is metastatic and distinct from her known metastatic uterine malignancy, it is certainly possible; the patient received chemotherapy, which can increase the risk of developing some cancers.⁵ In women, the most frequent tumors to metastasize to bone include lung

and breast malignancies.^{3,4}

Regarding her prior diagnosis of metastatic uterine malignancy, it would be important to review her prior surgical resections, biopsies, and cytology and reports, if they are available, to assist in determining what type of uterine tumor she had previously. Malignant tumors of uterine corpus can be broadly split into carcinomas and sarcomas.^{6,7} Carcinomas arise from the glands in the endometrium lining the endometrial canal of the uterus. Sarcomas form from the mesenchymal tissues of the uterus, of which there are several types: endometrial stroma, which surrounds the endometrial glands in the innermost layer of the uterine wall; uterine muscle, also called the myometrium; and fibrovascular connective tissue interspersed in the uterine muscle and serosa.

What diagnostic testing is available for this patient?

Imaging of the bone lesions in the spine and hips would be the best first initial test. X-rays of these areas can be performed as a screening test, followed by computed tomography (CT) and/or magnetic resonance imaging (MRI), which provide better resolution.

If a mass is seen on imaging, a biopsy and/or fine needle aspiration should be performed next. Imaging can suggest differential diagnoses based on the appearance, size, and location of the mass, but a tissue sample is required to make a definitive diagnosis. For the pathologist reviewing the resulting specimen, it would be important to review prior histopathologic records to determine the type of the patient's prior uterine malignancy, as mentioned above.

Although not essential in this case, ordering a complete blood count and erythrocyte sedimentation rate may also be considered. Leukocytosis with a predominance of neutrophils and an elevated erythrocyte sedimentation rate may be supportive of osteomyelitis.

Diagnostic findings, Part 2

The patient undergoes a CT scan of the spine with contrast, with representative images of right iliac crest lesion and T10 vertebral lesion shown in Fig. 1. Radiographically, both lesions are described as osteoblastic, and demonstrate increased sclerosis compared to prior imaging studies.

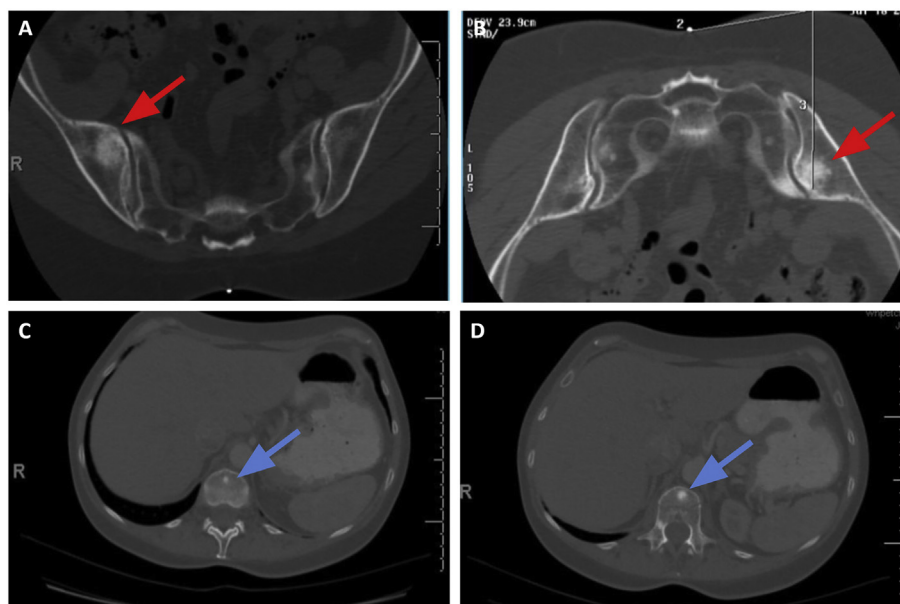


Fig. 1. Computed tomography (CT) scans demonstrating contrast-enhancing lesions in the right iliac crest (A and B, red arrows) and T10 vertebral body (C and D, blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Questions/discussion points, Part 2

What method should be used to obtain a definitive diagnosis and staging?

To establish a definitive diagnosis, sampling of the lesions for pathologic assessment should be performed. This can be done with either a core needle biopsy (CNB) or a fine needle aspiration biopsy (FNAB). When sampling bone, guidance by imaging modality, such as CT or MRI, is often used to ensure the needle trajectory is appropriate, and to minimize the need for re-biopsy. Employing rapid on-site cytologic assessment at the time of biopsy can help guide radiologists, and improve diagnostic yield.^{8–10} If the goal is diagnosis and staging, and not surgical removal of the metastatic foci, CNB and FNAB are practical methods of tissue sampling that carry a lower risk of infection and bleeding compared to surgical resection. Both CNB and FNAB enable immediate assessment of samples with opportunity for triage for ancillary studies.^{7–10} There are advantages and disadvantages to CNB versus FNAB as sampling techniques. Both are excellent methods in obtaining diagnostic material. However, both also share the risk of sampling error, given that only a small amount of lesional material is obtained. In contrast to FNAB, CNB is a method of obtaining small intact tissue fragments, and therefore, it has the advantage of having more material that maintain intact architectural clues. On-site assessment is achieved by doing a touch preparation, and these are evaluated similarly to FNABs. FNAB is less costly, minimally invasive, and can sample multiple tissue planes without disrupting tissue integrity. However, lack of pathologist familiarity with appearance of soft tissues on smear and the requirement for regular exposure to soft tissue smear morphology limits the use of FNA in community settings.¹⁰

In this patient, core biopsies with touch preparation of both the right iliac and T10 vertebral masses are performed, and representative images from these biopsies are shown in Fig. 2. The biopsies from both sites demonstrate abundant cells with round to oval nuclei, fine chromatin, and scant cytoplasm. The cells are frequently encountered in tight

clusters with occasional intervening naked nuclei.

The pathologist reviewed the patient's prior pathology records and determined that the patient had been diagnosed with metastatic low grade endometrial stromal sarcoma. The pathologist also reviewed the morphology of the patient's prior hysterectomy specimen, which demonstrated identical tumor cells to those present in the current specimens.

What types of tumors can develop from the uterine mesenchyme?

The uterine mesenchymal tissues include endometrial stroma, the myometrium, and the fibrovascular tissue of the serosa, as depicted in Fig. 3. Each of these tissues may give rise to both benign and malignant neoplasms (see Table 1).^{6,7} Endometrial stromal sarcoma arises from the endometrial stroma. Endometrial stromal nodules (ESN) can also arise from endometrial stroma; these are well-demarcated masses that have cells that are similar to usual proliferative-phase endometrium. ESN can harbor a *JAZF1-SUZ12* fusion, which can also be identified in endometrial stromal sarcomas (ESS), but they do not exhibit aggressive features like lymphovascular invasion or infiltrative borders. Patients with ESNs have an excellent prognosis.^{6,7}

The myometrium can give rise to uterine leiomyomas, leiomyosarcomas, and smooth muscle tumors of uncertain malignant potential (STUMPs). Leiomyomas are the most common uterine tumors, and they consist of circumscribed benign neoplasms of smooth muscle cells.^{6,7} They can be present in the submucosa, within the uterine wall (intramural), or in the subserosal area. They are most common in women of reproductive age. Their growth is stimulated by estrogen and progesterone. After menopause, when levels of these hormones are decreased, leiomyomas often shrink in size. Leiomyosarcomas are malignant smooth muscle tumors that can demonstrate spindled, epithelioid, or myxoid morphology. These tumors are the most common type of uterine sarcoma. Leiomyosarcomas are often large, and exhibit hemorrhage and necrosis. At least two of the following three criteria must be met to diagnose a leiomyosarcoma: significant cytologic atypia, more than 4

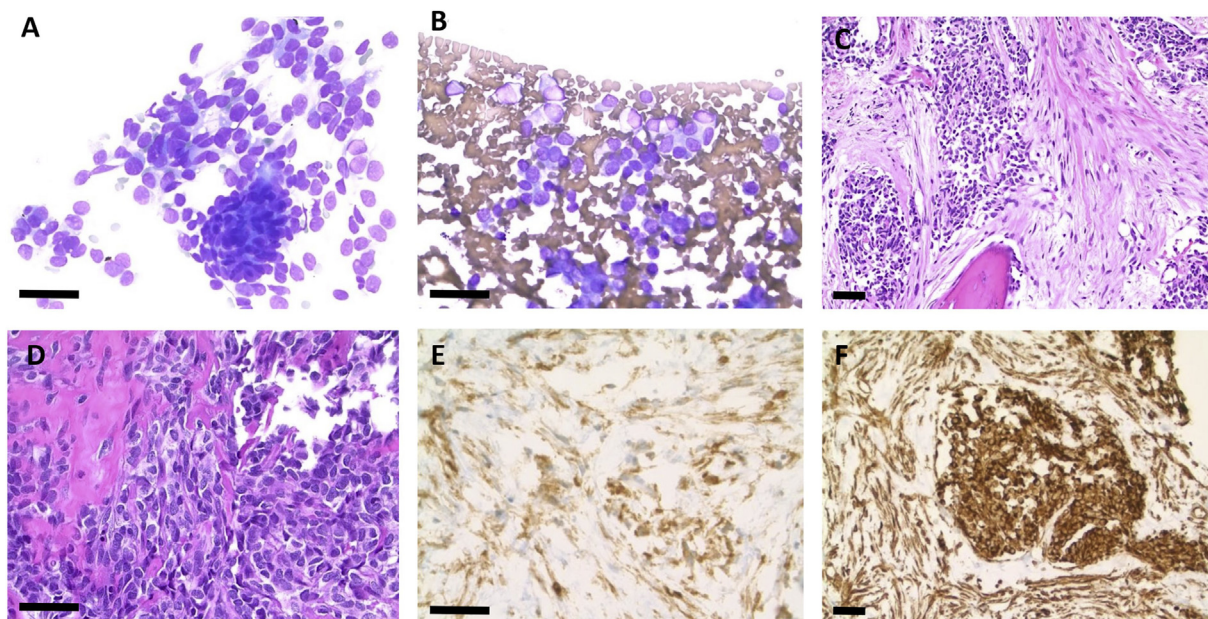


Fig. 2. A–C. Core needle biopsies of the right iliac bone lesion. A & B, cytologic features: Loose aggregates and dispersed single cells exhibiting enlarged nuclei with fine chromatin and scant to moderate amount of cytoplasm, (Touch preparation slides, Diff–Quik stain, Bar = 42 μ m). C: Histologic sections demonstrate a mostly fibrotic marrow space with infiltration by sheets and clusters of small round blue cells with hyperchromatic nuclei (hematoxylin and eosin, Bar = 70 μ m). D–F. Core needle biopsies of the T10 vertebral lesion. D: Tumor cells with hyperchromatic nuclei and inconspicuous nucleoli, arranged in a patternless proliferation. (hematoxylin & eosin, Bar = 70 μ m). E & F, immunohistochemical features. The tumor cells show positivity for CD10 (immunohistochemical stain, Bar = 70 μ m) and vimentin (immunohistochemical stain, Bar = 70 μ m). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

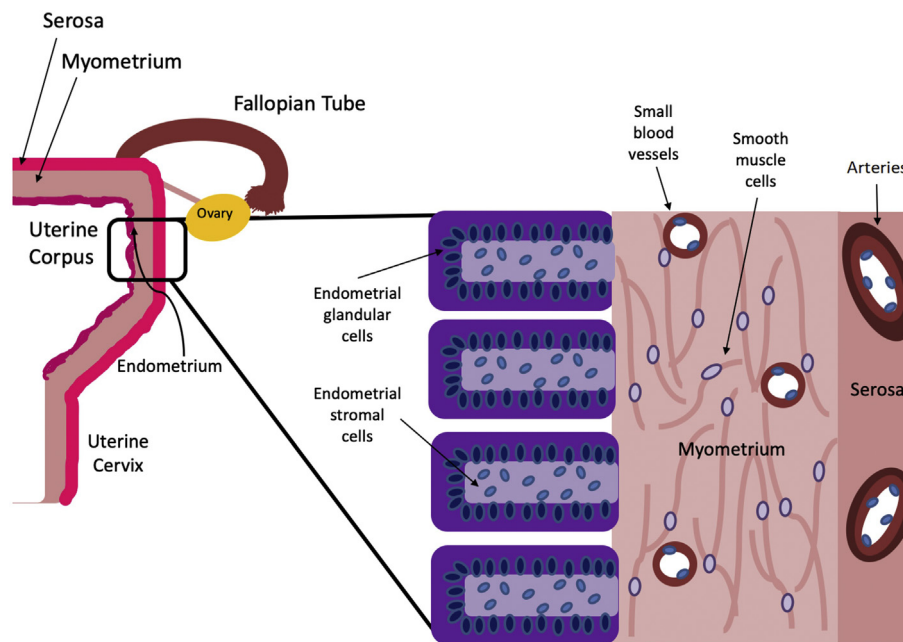


Fig. 3. Schematic of the upper gynecologic tract, and the different uterine mesenchymal cells—endometrial stroma, the myometrium, and the fibrovascular tissue of the serosa.

mitoses per mm², and tumor cell necrosis.^{6,7} Leiomyomas and leiomyosarcomas make up the two ends of the spectrum of uterine smooth muscle tumors, whereas STUMPs have intermediate features between the two. STUMPs will show some features that are compatible with a leiomyosarcoma, such as increased mitotic activity, necrosis, or cytologic atypia, but will fall short of a diagnosis of leiomyosarcoma.^{6,7}

There are some uterine mesenchymal tumors, which have unclear origin, namely undifferentiated uterine sarcoma, uterine rhabdomyosarcoma, *SMARCA4*-deficient sarcoma, and uterine tumor resembling ovarian sex cord tumor.^{6,7} Undifferentiated uterine sarcoma is a malignant mesenchymal neoplasm with uniform or pleomorphic cytology, and with no evidence of differentiation toward a specific mesenchymal cell type. *SMARCA4*-deficient uterine sarcoma is a malignancy with extensive morphological overlap with undifferentiated uterine sarcoma, but shows lack of expression of the BRG1 protein, the product of the *SMARCA4* gene, which regulates chromatin remodeling.^{6,7} Uterine rhabdomyosarcomas are malignant tumors that show skeletal muscle differentiation and may have rhabdomyoblasts and striated cells.^{6,7} Uterine tumor resembling ovarian sex cord tumor bears morphologic similarity to ovarian sex cord stromal tumors in its growth pattern. Undifferentiated

uterine sarcoma is considered a diagnosis of exclusion, as such, all other possible diagnoses must be ruled out before making this diagnosis.^{6,7}

Perivascular epithelioid cell tumors (PEComas) arise from perivascular cells that demonstrate both smooth muscle and melanocytic differentiation.⁶ These tumors may show loss of function mutation in *TSC1/2* or harbor *TFE3* fusions. Inflammatory myofibroblastic tumors (IMFTs) consist of myofibroblasts and fibroblasts with a component of inflammatory cells. Cytoplasmic positivity of the ALK immunohistochemical stain has high sensitivity and specificity for IMFTs. The vast majority of PEComas and IMFTs are benign, with only rare malignant versions of these tumors described.⁶ Exceedingly rare uterine mesenchymal tumors include vascular neoplasms, lipomatous tumors, alveolar soft part sarcoma, solitary fibrous tumor, nerve sheath tumors, and giant cell tumor.⁶

A diagnostic distinction must be made between uterine sarcomas and biphasic lesions, such as adenosarcoma or carcinosarcoma. Carcinosarcomas are defined as biphasic tumors exhibiting both malignant glandular and mesenchymal components.^{6,7} They are considered as a dedifferentiated variants of endometrial carcinomas, and as such, they behave more similarly to endometrial adenocarcinomas,

Table 1
Uterine mesenchymal cell types and associated neoplasms.

Tissue	Cell type	Associated benign neoplasms	Associated malignant neoplasms
Endometrial stroma	Endometrial stromal cells	Endometrial stromal nodule	Endometrial stromal sarcoma (low-grade and high-grade)
Myometrium	Smooth muscle cells	Leiomyoma	Leiomyosarcoma, smooth muscle tumor of uncertain malignant potential (STUMP) ^a
Unclear origin		Uterine tumor resembling ovarian sex cord tumor	Undifferentiated uterine sarcoma, uterine rhabdomyosarcoma, <i>SMARCA4</i> -deficient sarcoma
Blood vessels	Perivascular cells	Perivascular epithelioid tumor (PEComa) ^b	Angiosarcoma
Fibrous tissue	Myofibroblasts, fibroblasts	Inflammatory myofibroblastic tumor (IMFT) ^b , solitary fibrous tumor ^b	Fibrosarcoma

^a Smooth muscle tumors of uncertain malignant potential often behave in a malignant manner and are therefore placed in the malignant neoplasm category.

^b The vast majority of these tumors behave in a benign fashion and therefore this tumor is placed in the benign neoplasm category.

rather than uterine sarcomas.¹¹ Adenosarcomas, on the other hand, have a malignant stromal component but have benign appearing glands.^{6,7}

What is endometrial stromal sarcoma?

Endometrial stromal sarcoma (ESS) is a mesenchymal tumor arising from the uterine endometrium, and consists of malignant stromal cells that are similar in appearance to the usual proliferative-phase endometrial stroma, but exhibit an infiltrative growth pattern and can often display lymphovascular invasion.^{6,7} It affects patients in a wide age range, including those in their teens, and up to the 8th decade. Patients typically present with abnormal uterine bleeding, pelvic pain, or pressure, but a quarter of patients may be asymptomatic.⁹ Patients may have metastatic disease in the ovaries, lymph nodes, or lungs at presentation. Risk factors for ESS include prolonged exposure to estrogen and pelvic irradiation.^{6,7} Gross examination of the tumors typically demonstrates yellow-tan uterine wall nodules with infiltrative growth into the myometrium. Prominent “worm-like” plugs, which represent intravascular tumor are characteristic.^{6,7}

ESS is further subclassified as low or high grade, with grade referring to how atypical the malignant stromal cells appear. The cells of low grade ESS are usually indistinguishable from normal endometrial stromal cells. They exhibit uniform sheets of round to oval nuclei, but unlike normal endometrial stroma, low grade ESS forms nodules, and shows invasive growth.^{6,7,12,13} These histologic features are seen in the patient's hysterectomy specimen in Fig. 4. The background is usually clean, without necrosis and a hyaline matrix may be present. In high grade ESS, the tumor cells have angular nuclear contours, conspicuous nucleoli, and vesicular chromatin.^{6,7,12,13} Spindled to epithelioid “comet” cells may be present in cytology preparations.¹² In addition to different cytomorphologic features, low and high grade ESS have been characterized by different chromosomal translocations: most low grade ESS patients show the *JAZF1-SUZ12* fusion, whereas high grade ESS harbor *YWHAE-NUTM2A/B* fusions, *ZC3H7B-BCOR* fusions, or *BCOR* internal tandem duplications.^{6,7} Demonstration of these molecular anomalies aid in the diagnosis of morphologically unusual cases, or those that occur in unusual locations.

Diagnostic findings, Part 3

Several immunohistochemical stains are performed on the biopsy specimen, and the tumor was found to be diffusely positive for CD10, ER, and vimentin, as shown in Fig. 2. The tumor cells are patchy positive for AE1/AE3, and negative for PAX-8, GATA-3, TTF-1 and synaptophysin. This immunophenotype matches the staining pattern of the patient's known low grade endometrial stromal sarcoma.

Questions/discussion points, Part 3

What ancillary tests can be used to differentiate between endometrial stromal sarcoma and other uterine mesenchymal tumors?

The combination of immunohistochemical markers and molecular testing for genetic alterations can aid in the distinction between uterine mesenchymal tumors.^{6,7} The immunoprofile of low grade ESS typically express CD10, ER, and PR, but not Cyclin D1, whereas high grade ESS usually demonstrate variable ER and PR expression. Low grade endometrial stromal sarcomas can also variably express broad-spectrum keratins, inhibin, calretinin, WT1, CD99, melan-A, as well as smooth muscle markers. As mentioned previously, low grade ESS often harbor *JAZF1-SUZ12* fusion, whereas high grade ESS harbor *YWHAE-NUTM2A/B* fusions, *ZC3H7B-BCOR* fusions, or *BCOR* internal tandem duplications.^{6,7}

Leiomyomas, STUMPs, and leiomyosarcomas will show expression of smooth muscle markers like desmin, caldesmon, and smooth muscle actin, which may be variable. Regarding molecular alterations, leiomyomas may exhibit *MED12*, *HMG2/1*, and *COL4A5/6* alterations. *MED12* alterations can also be seen in some STUMPs.^{6,7}

Uterine tumor resembling ovarian sex cord tumors usually show positivity for sex cord stromal markers like inhibin, calretinin, WT1, CD56, CD99, and SF1.^{6,7} They may also have gene rearrangements involving *ESR1* or *GREB1*. Undifferentiated uterine sarcomas have a non-specific immunoprofile, variable positivity for p53, p16, and CD10, lack of the gene fusions seen with other sarcomas, and negativity for ER and PR. Rhabdomyosarcomas exhibit desmin, myogenin, and myoD1 positivity, whereas *SMARCA4*-deficient sarcomas demonstrate loss of BRG1 protein expression.^{6,7}

What is the prognosis and treatment of endometrial stromal sarcoma?

Similar to other malignancies, the prognosis and treatment of ESS depend on its grade and stage at the time of diagnosis. Low grade ESS have a relatively indolent course, even if patients have locoregional recurrence.⁷ Clinical staging is a critical prognostic factor of low grade ESS, with poorer prognosis seen in patients in stage III and IV disease.⁷ Clinical elements that may portend a negative prognosis include increased parity, age over 53 years, postmenopausal state, and African American race.⁷ The mainstay of therapy is total abdominal hysterectomy with bilateral salpingo-oophorectomy. Radiotherapy, chemotherapy, and hormonal therapy may play a role in the treatment of patients with recurrent or metastatic disease.¹⁰ Patients with high grade ESS, whose tumors harbor the *YWHAE-NUTM2A/B* fusion may respond to treatment with anthracycline.⁶

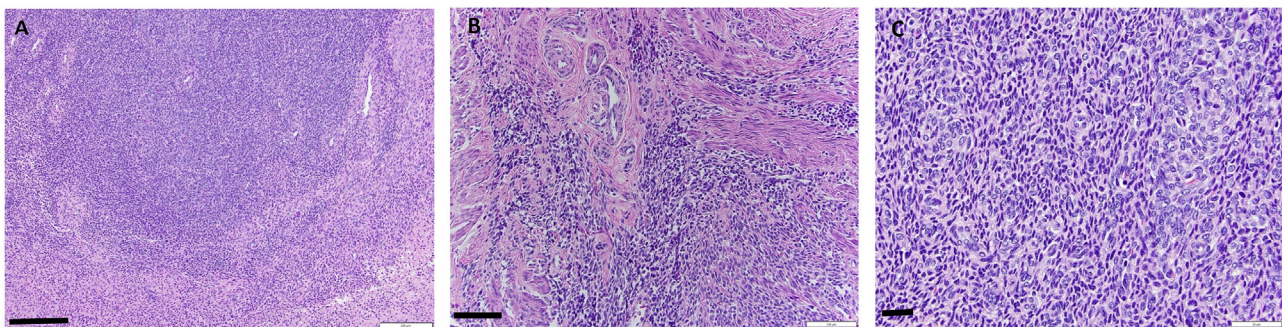


Fig. 4. Micrographs from the hysterectomy specimen demonstrating low grade endometrial stromal sarcoma. A: Low power image showing irregular nests of tumor cells resembling proliferative-phase endometrial stromal cells (hematoxylin & eosin, Bar = 200 μ m). B: Intermediate magnification demonstrates hyperchromatic tumor cells infiltrating in between myometrial smooth muscle bundles (hematoxylin & eosin, Bar = 100 μ m). C: Higher magnification shows the hyperchromatic cells with scant cytoplasm (hematoxylin & eosin, Bar = 50 μ m).

Patient follow-up

After diagnosis with metastatic endometrial stromal sarcoma to the T10 vertebra and right iliac crest, the patient undergoes external beam radiation to vertebrae T8 through T12 and receives two cycles of chemotherapy with doxorubicin. She tolerates the treatment well and her metastatic disease has decreased in size.

Teaching points

- The differential diagnosis for bony masses in an adult female include inflammatory conditions, trauma, and benign, malignant, primary, and metastatic tumors.
- Malignant neoplasms of the uterine corpus are divided into carcinomas, which arise from endometrial glands, and sarcomas, which arise from mesenchymal tissue.
- There are several types of uterine mesenchyme, including endometrial stroma, myometrium, and fibrovascular tissue. Cell types from each of these tissues can give rise to various benign and malignant neoplasms.
- Benign neoplasms arising from uterine mesenchyme include endometrial stromal nodule, leiomyoma, perivascular epithelioid tumor, and inflammatory myofibroblastic tumor.
- Malignant neoplasms arising from uterine mesenchyme include endometrial stromal sarcoma, leiomyosarcoma, undifferentiated sarcoma, uterine rhabdomyosarcoma, and SMARCA4-deficient sarcoma.
- Fine needle aspiration and core surgical biopsy are useful techniques to employ in obtaining samples for cancer staging; each method has its own advantages and shortcomings.
- Endometrial stromal neoplasia comprises a spectrum from benign tumors, such as endometrial stromal nodules (ESN) to malignant endometrial stromal sarcomas, both low and high grade.
- Endometrial stromal sarcomas (ESS) arise from endometrial stromal cells, display infiltrative growth into the myometrium, and can exhibit “worm-like” vascular plugs of tumor cells that can even be identified grossly.
- Immunohistochemical stains that are frequently expressed in ESS include CD10, cyclin D1, and estrogen receptor.
- Low-grade ESS are characterized by *JAZF1-SUZ12* fusions, whereas high grade ESS harbor *YWHAE-NUTM2A/B* fusions, *ZC3H7B-BCOR* fusions, or *BCOR* internal tandem duplications.

- Low-grade ESS tend to have an indolent course, but may have locoregional recurrence or distant metastases.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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