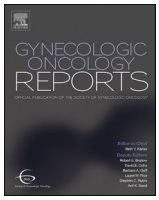
Gynecologic Oncology Reports 54 (2024) 101422

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



Case report

Metastatic malignant peripheral nerve sheath tumor of the uterus and cervix: Diagnostic Challenges, prognostic determinants and treatment

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1 Introduction

Uterine leiomyomas are the most common neoplasm in reproductive-aged women. Surgical management with myomectomy in order to preserve the uterus for future childbearing is common practice. While uterine leiomyomas are common, uterine sarcomas also present in reproductive-aged women. Uterine sarcomas often present with nonspecific findings such as abnormal bleeding, pelvic pain or pressure. Delineating the two neoplasms in reproductive-aged women can be difficult as their clinical manifestations are similar. The decision to preserve the uterus needs consideration of the low, yet real, risk of uterine sarcoma preoperatively.

Uterine sarcomas rarity was elucidated in a SEER database study estimating the incidence of 2.8 per 100,000 person years among women aged 30–79, which is corrected for hysterectomy prevalence (Clarke et al., 2019). The World Health Organization (WHO) classification of uterine tumors classifies mesenchymal tumors into well-recognized categories: smooth muscle tumors which include leiomyosarcomas and endometrial stromal sarcomas and related tumors. The less recognized category of miscellaneous mesenchymal tumors is rarely encountered, clinically. This category include vascular tumors, lipomatous tumors, alveolar soft part sarcoma, solitary fibrous tumor, giant cell tumor, and nerve sheath tumors (Parkash et al., 2023). Malignant peripheral nerve sheath tumor (MPNST) may be of interest to the practicing gynecologic oncologist as there is no preoperative distinction of pathology on clinical exam or preoperative imaging. MPNST arising in the female reproductive tract is extremely rare, with detailed information limited to fewer than 30 case reports (Sangiorgio et al., 2018; Sengar Hajari et al., 2015). Of these case reports, MPNST has been reported in the cervix, uterine corpus, vagina, and vulva (Rodriguez et al., 2006; Guzin et al., 2021; Maglione et al., 2002). Our case report presents a reproductive-age female diagnosed with MPNST following uterine myomectomy. The tumor had rapid dissemination to the pelvic peritoneum, pelvic retroperitoneum, and omentum following morcellation of presumed fibroids during myomectomy.

2 Case

A 29-year-old female gravida 0 with a history of uterine fibroids presented with a six-month history of worsening pelvic pressure and abnormal uterine bleeding resulting in severe acute-on-chronic anemia, requiring multiple hospitalizations for blood transfusions. Fig. 1 demonstrates the ultrasound findings during the initial presentation to the emergency room. A large heterogeneous, predominantly hypoechoic mass centered in the cervix extended into the lower uterine segment. A pelvic exam revealed dark blood and clots. The cervix was unable to be visualized, but on palpation, there was no cervical mass.

The patient underwent an abdominal myomectomy after expressing interest in maintaining fertility during her 2nd hospitalization for symptomatic anemia due to excessive bleeding. Intraoperative findings included an enlarged uterus approximately 22 weeks in size with a significant leiomyoma burden. Many of the neoplasms appeared to be degenerated. The abdomen and pelvic cavity appeared normal, with no evidence of adhesions or disease. Given the large size of the uterus and small surgical incision, many large fibroids/masses had to be morcellated using a scalpel during their extraction. The patient was discharged home on postoperative day one in stable condition. The final pathology, shown in Figs. 2a and 2b, was reviewed by an expert sarcoma pathologist and revealed the diagnosis of a malignant peripheral nerve sheath tumor. Specifically, the tumor had notable hypercellular and less cellular myxoid features. It appeared cytologically high grade, although the mitotic index and proliferative activity on a submitted Ki-67 immunostain were not significantly increased as expected. A panel of immunostains were performed and the tumor cells are positive for S100

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https://doi.org/10.1016/j.gore.2024.101422
Received 14 February 2024; Received in revised form 13 May 2024; Accepted 17 May 2024
Available online 27 May 2024

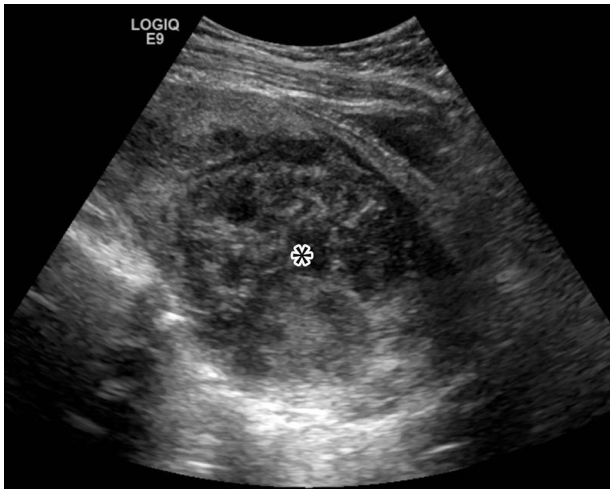

Fig. 1. Transabdominal grayscale ultrasound image along the long axis of the uterus shows a large heterogeneous predominantly hypoechoic mass centered in the cervix extending into the lower uterine segment (*).

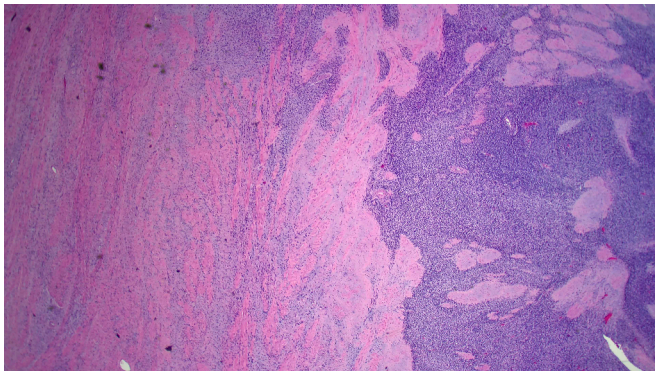

Fig. 2a. Low power view of malignant peripheral nerve sheath tumor infiltrating into myometrium.

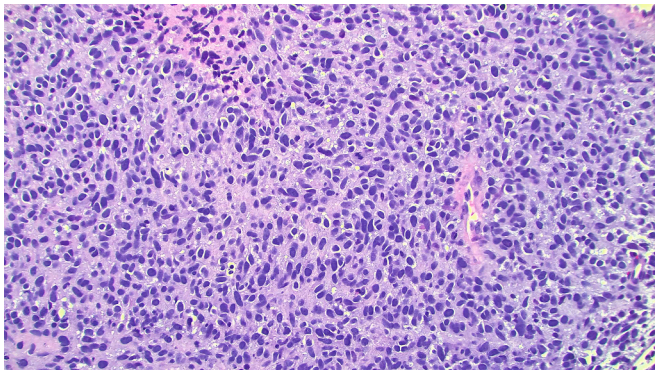

Fig. 2b. High power view of the malignant neoplasm with pleomorphic nuclei, high N/C ratio and brisk mitotic activity.

(diffuse expression), SOX10 (extensive expression) and negative for muscle markers (desmin, smooth muscle actin, myogenin), ER, PR, Melan A, and HMB45. Notably, although malignant melanoma was considered as a potential etiology due to the diffuse and extensive S100 and SOX10 expression, the lack of HMB-45 expression and the lack of Melan-A expression, as well as the overall morphology, were more consistent with MPNST.

Based on intraoperative findings, the disease was suspected to be confined to the uterus. The patient was then referred to gynecologic oncology for evaluation and management. Gynecologic oncologic consultation recommended a robotic-assisted total hysterectomy and bilateral salpingectomy, with consideration of ovary preservation for future fertility via surrogate following reproductive endocrinology and infertility consultation. The preoperative CT scan revealed no evidence of metastatic or peritoneal disease. Planned definitive surgical treatment occurred within 4 weeks of surgery. Immediate intraoperative findings revealed extensive metastatic disease in the peritoneal cavity and subperitoneal tissues had evidence of invasion. Multiple peritoneal biopsies were performed. The upper abdominal area was explored, including the right and left hemidiaphragm, and was without gross disease. The right ovary and fallopian tube appeared enlarged. A right salpingo-oophorectomy was then performed for tissue diagnosis as the patient's uterine disease was deemed inoperable at the time of her surgery due to pelvic sidewall involvement.

In this subsequent surgery, besides multiple foci of abdominal wall and pelvic peritoneal tumor nodules, the tumor also involved adnexa/paratubal tissue while the ovary was spared. A small focus of low-grade spindle cell proliferation is noted in the fallopian tube mucosa, which is suggestive of a potential precursor type lesion, neurofibroma. Repeated immunostains show a similar immunoprofile seen in the previous specimen. In summary, although the tumor was initially discovered in the routine myomectomy procedure for leiomyoma, in fact, it may arise from the right fallopian tube areas or some other areas of the abdominal wall or pelvic peritoneum but present/manifest as uterine leiomyoma.

In this patient, intraoperative surgical findings exhibited peritoneal and intra-abdominal disease. First line systemic treatment was initiated with doxorubicin, ifosfamide and mesna for 3 cycles followed by progressive disease. Second line therapy with gemcitabine and docetaxel stabilized disease for 9 cycles. Unfortunately, this patient died of disease nearly one year from diagnosis.

3 Discussion

To our knowledge, all report cases of MPNST with cervical involvement have presented with a visible cervical mass on examination; while there are no published reports following uterine myomectomy.

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon neoplasm of neural origin that typically arises in the legs, arms, or trunk. In this setting, complete surgical excision with clear margins is the treatment of choice. We present a 29-year-old female with MPNST due to the rarity of tumor origin, the uterus and cervix. Investigation for potential genetic cause of this tumor via next-generation sequencing, did not reveal any genetic fusions or mutations. Neurofibromatosis type 1 (NF1), autosomal dominant mutation which results in loss of tumor suppressor gene neurofibromin, was also excluded (Farid et al., 2014). There is scant data on MPNST in reproductive age women who desire future fertility Neurofibromatosis type 1.

Case reports have found uterine and cervical MPNST after complaints of pelvic pain/pressure, abnormal uterine bleeding, and anemia and after screening pap smears with colposcopy. Diagnostic radiology can aid in diagnosis and preoperative planning; however, at times this could pose a further challenge due to frequent overlapping features of atypical fibroids and sarcomas on imaging. Pelvic MRI, including diffusion-weighted imaging (DWI), is the imaging modality of choice for differentiating benign versus malignant uterine masses (Smith et al., 2021). Malignant uterine masses typically demonstrate irregular borders with intermediate to high signal intensity on T2-weighted images. Additionally, there can be intrinsic hemorrhage which would be hyperintense on T1-weighted images and/or necrosis. Restricted diffusion is a commonly used differentiator between benign and malignant uterine masses. Masses that demonstrate abnormal restricted diffusion are hyperintense on DWI and hypointense on apparent diffusion coefficient (ADC) indicating hypercellularity (e.g., malignant tumors) (Bonde et al., 2022; Hindman et al., 2023). However, uterine fibroids

can show varying degrees of diffusion restriction depending on the amount of fibrosis, smooth muscle, and degeneration present, leading to a certain rate of misdiagnosis (Bonde et al., 2022). Despite these potential pitfalls, preoperative uterine mass imaging should include pelvic MRI with thorough evaluation by an expert pelvic MRI radiologist when available to give a more complete picture of the mass's malignant potential. In our patient, her acute blood loss requiring second hospitalization for blood transfusion omitted preoperative MRI. This patient went to the operating room for myomectomy during this hospitalization for presumed leiomyoma.

In addition to diagnostic challenges, surgical counseling and planning in reproductive-aged women with imaging suggestive of uterine sarcoma requires an "all or none" approach. Essentially, removal of the uterus intact is recommended for suspicious findings on pre-operative MRI while consideration for surgical removal of presumed leiomyomas with plan for leaving the uterus in situ is unadvisable. In our patient, planned myomectomy resulted in seeding of the peritoneum not only upstaging the patient but resulting in incurable disease. Consideration for consultation with a reproductive endocrinologist and infertility (REI) who specializes in oncofertility. Most options, if any, include assisted reproductive technology which is high cost, may require surrogate carrier and potential result in delay in cancer. Time is of the essence when considering surgery in reproductive-aged patients with suspicious findings on imaging (Walsh et al., 2017).

Treatment of gynecologic-origin MPNST is scarce. MPNST, in general, has been well-established as an aggressive chemo-resistant tumor. The prognosis is poor with high recurrence rates, even with early and multimodal treatment. Tumor metastasis is common. Prognostic factors are still being investigated, but adverse prognostic factors typically include the presence of NF1, large tumor size (greater than 5 cm), and positive surgical margins (Gupta et al., 2008). No clearly defined or widely reproducible molecular prognosticators have been demonstrated (Farid et al., 2014). One study of over 700 patients with localized MPNST demonstrated a median overall survival of 64 months; however, for patients with metastatic disease, median overall survival was a dismal eight months, with a 3-year survival rate of 9.2% (Xu et al., 2021).

Standard of care for female reproductive tract MPNST has not been determined due to its rarity. However, the treatment of choice for MPNST is complete surgical resection at diagnosis. Adjuvant radiation therapy has been shown to decrease local disease recurrence significantly but has had limited success in increasing long-term survival due to the aggressive nature of the tumor (Stucky et al., 2012). Chemotherapy may be considered for metastatic or unresectable disease, however, effectiveness has not been proven in the literature (Stucky et al., 2012). Recent trials have shown some MPNST sensitivity to ifosfamide and etoposide combinations (Higham et al., 2017). However, MPNST and most soft tissue sarcomas are generally regarded as chemotherapy-insensitive (Chuang et al., 2020). Targeted gene therapy treatments are also being considered to treat MPNST in gynecological cases and in general. A recent case report of MPNST of the cervix advocates for more in-depth molecular testing of this cancer (Wells et al., 2019). They report on a patient who was found to have a TPM3-NTRK1 fusion mutation, which is targeted by Larotrectinib. This oral medication was FDA-approved in 2018 as therapy for solid tumors that possess the NTRK gene fusion and have been refractory to other first-line options or for patients who are poor surgical candidates (Wells et al., 2019). Even metastatic NTRK translocated sarcomas have demonstrated some improvement from NTRK-targeted therapies (Doebele et al., 2015). This positive clinical response indicates the possibility of other actionable molecular targets for this disease.

Overcalling of atypical leiomyomas as malignant entities can mean irreversible surgery with hysterectomy in a woman who might desire future fertility. Conversely, underdiagnosis of potential uterine sarcoma can result in delayed diagnosis and inappropriate management with potentially devastating consequences, due to the aggressive nature of malignant uterine sarcomas. It is imperative to have a thorough review of the patient's history, preoperative imaging, and a high index of suspicion to provide timely and appropriate surgical and reproductive planning.

CRediT authorship contribution statement

Anne Laird: Writing – review & editing, Writing – original draft. **Olivia Casas Diaz:** Writing – original draft, Conceptualization. **Faye Gao:** Writing – original draft. **Nancy Kim:** Writing – original draft. **Ebony Hoskins:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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