



## Case report

## Sixteen year-old with leiomyosarcoma in a prior benign myomectomy site

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## ABSTRACT

Uterine leiomyosarcoma in a prior myomectomy site is a rare phenomenon. We report an unusual case of a leiomyosarcoma arising six months post myomectomy in a 16-year old female.

## 1. Introduction

Uterine leiomyomas are the most common gynecologic tumors in the United States. These benign tumors arise from overgrowth of smooth muscle and connective tissue within the uterus and are frequently diagnosed in childbearing years (Baird et al., 2003). Leiomyomas can undergo various degenerative changes, however malignant transformation is rare (Al Ansari et al., 2012; Yanai et al., 2010).

Uterine leiomyosarcoma (ULMS) is a rare malignancy of smooth muscle that typically occurs in women over age 50, with isolated cases reported in the pediatric literature. ULMS is diagnosed using the Stanford histologic criteria: coagulative necrosis, cellular atypia, elevated mitotic rate of greater than 10 mitotic figures (MF) per 10 high power field (HPF) (Bell et al., 1994). Most cases of ULMS arise de novo with limited reports of ULMS arising in leiomyoma (Mittal et al., 2009). Herein we report the case of a 16-year old Hispanic female who developed a leiomyosarcoma at prior myomectomy site 6 months after initial surgery.

## 2. Case

A 16 year-old, healthy, Hispanic, gravida 0 female presented to the Emergency Department (ED) with abdominal pain and distension. Her gynecological history was unremarkable and included normal menstrual cycles and no prior use of hormones. She denied any medical conditions, prior surgeries, or family history of malignancy.

The patient's vital signs were normal. Physical examination revealed a firm, palpable lower abdominal mass. Transvaginal ultrasound and CT of the abdomen and pelvis revealed a solid, homogeneous pelvic  $14 \times 13 \times 9$  cm mass that was separate from a normal appearing uterus and ovaries (Fig. 1A). An MRI of the abdomen and pelvis demonstrated a  $15 \times 10 \times 12$  cm uterine mass consistent with leiomyoma. Tumor markers including AFP, LDH and  $\beta$ -hCG were all within normal limits.

The patient was admitted to pediatric oncology and a subsequent diagnostic laparoscopy revealed a pelvic mass arising from the posterior aspect of the uterus. The mass was biopsied and final pathology revealed benign leiomyoma while cytologic evaluation of the ascites was negative for malignancy. Intraoperative findings revealed a large, hypervascular, necrotic mass encasing the posterior aspect of the uterus and extending

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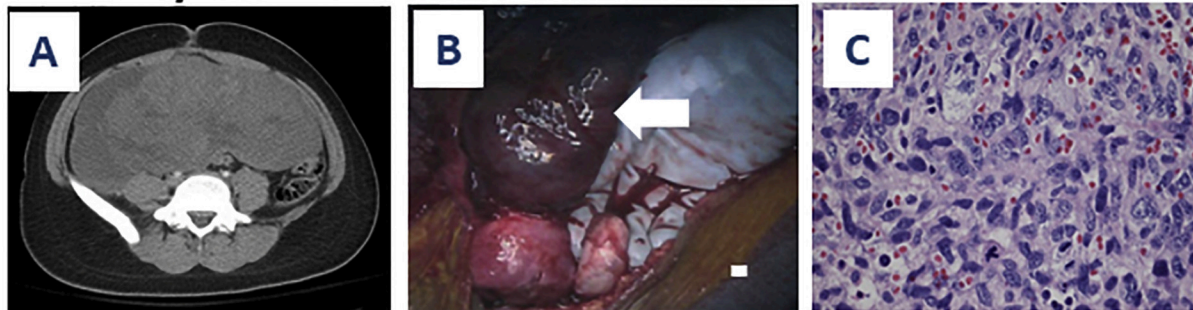
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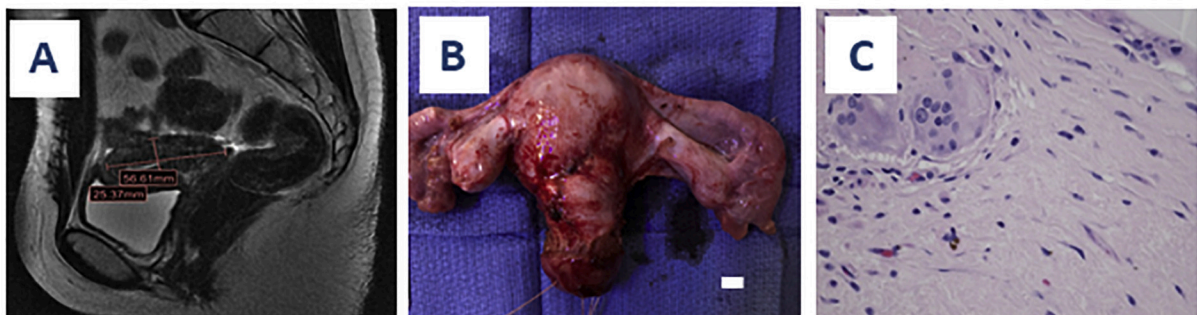
## 1. Leiomyoma



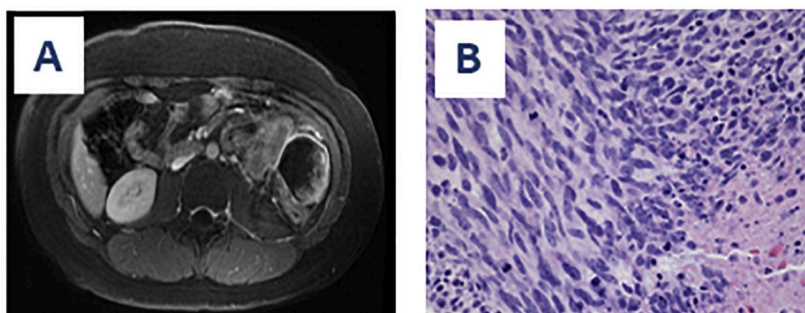
## 2. Leiomyosarcoma



## 3. No Residual Leiomyosarcoma



## 4. Recurrent Leiomyosarcoma



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**Fig. 1.** First hospital admission (1A – 1C). Radiographic image from CT of mass on day 0 (1A), gross images from myomectomy performed 8 days from the laparoscopy pelvic biopsy (1B) and histological image of myomectomy on day 8 (1C). Second hospital admission. Radiographic image of CT abdomen/pelvis of second pelvic mass leiomyosarcoma on day 185 (2A), gross image of tumor resection performed 182 days from myomectomy (2B) and histological image of primary tumor resection on day 190 (2C). Third hospital admission (3A–3C). Radiographic image from the MRI prior to staging surgery on day 317 (3A), gross image from staging surgery performed 126 days from primary tumor resection (3B) and histological image from staging surgery on day 316 (3C). Fourth hospital admission (4A–4B). Radiographic image from the MRI of reoccurrence of malignancy (4A) and histological image of recurrent abdominal tumor debulking surgery on day 500 (4B). At initial presentation, the patient's CT showed a  $14 \times 13 \times 9$  cm midline, solid mass thought to be separate from a normal appearing uterus and ovaries on day 0 (1A). During the myomectomy, the uterus was noted to have two previous laparoscopy biopsied sites where there was protruding fibroid with active bleeding (the magnification bar in panel 1B measures 1 cm) (1B). Myomectomy showing leiomyoma comprised of bland spindle cells with no atypia, no necrosis, and only rare mitotic figures ( $400\times$ ) (1C). When the patient presented a second time to the hospital, a CT of the abdomen/pelvis visualized a new second pelvic mass that was a  $21 \times 10 \times 18$  cm that appeared heterogenous with cystic and solid components (2A). During the sarcoma resection, the tumor was noted to arise from the posterior aspect of the uterus with normal appearing adnexa (2B) and the large tumor notably ruptured at the time of removal due to necrotic, friable tissue. The magnification bar in panel 2B measures 1 cm and arrow highlights the tumor. Resection showing transformation of the uterine mass into a leiomyosarcoma composed of pleomorphic tumor cells with marked cytologic atypia, numerous mitotic figures (up to 14 MF/10 HPF), and tumor cell necrosis (not shown) ( $400\times$ ) (2C). Prior to staging surgery, an MRI illustrated no detectable residual or current pelvic mass, and the uterus measured  $6 \times 2.5 \times 3.7$  cm (3A). Grossly normal morphology of uterus, cervix and bilateral adnexa, the magnification bar in panel 3B measures 1 cm (3B). Post therapy hysterectomy showing no residual leiomyosarcoma; fibrosis and prior procedure changes ( $400\times$ ) (3C). Recurrence of malignancy on day 490 as MRI showed a  $4.5 \times 3.7$  cm heterogeneous mass within the left lateral abdomen (4A), a  $2.4 \times 2.0$  cm mass in left lower quadrant (not pictured), and small 0.9 cm mass posterior to the right hepatic lobe inferiorly (not pictured). Foci of recurrent high grade leiomyosarcoma (4B) composed of atypical cells with abundant mitotic figures and tumor cell necrosis ( $400\times$ ).

from the uterine fundus to the cervical os (Fig. 1B). A complete abdominal myomectomy was subsequently performed, and the patient's postoperative recovery was uncomplicated. Final pathology revealed a benign, cellular leiomyoma with hydropic change (Fig. 1C). Immunohistochemical stains for succinate dehydrogenase and fumarate hydrate were positive, excluding possibility of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) associated neoplasm. Additionally, immunostains for CD10, ALK1, myogenin, and HMB45 were negative, ruling out the possibility of endometrial stromal sarcoma, inflammatory myofibroblastic tumor, and PEComa respectively. Classical karyotyping revealed 46,XX, der(14)t(12;14)(q15;q24), der(15)del(15)(q11.2q15)inv.(15)(q21;q26)[15]/46,idem,t(7;13)(p11.2;q11.2)/46,XX.

Approximately six months later, the patient represented to the emergency room with abdominal pain and shortness of breath. She was hypotensive and tachycardic. Physical exam revealed a diffusely tender abdomen with a palpable abdominal mass. Laboratory evaluation demonstrated a drop in hemoglobin from 9 g/dL to 7 g/dL over five hours. Tumor markers were again within normal limits. A CT of the abdomen and pelvis revealed a  $21 \times 10 \times 18$  cm solid and cystic abdominal mass and a small amount of ascites (Fig. 1(2A)). The patient was transfused with packed red blood cells and underwent an exploratory laparotomy given concern for acute intraabdominal bleeding.

A  $20 \times 10 \times 18$  cm abdominal mass projecting from the posterior aspect of the uterus and a small amount of blood-tinged ascites was encountered intraoperatively (Fig. 1(2B)). The mass ruptured at the time of removal, demonstrating necrotic contents and blood clot. The remaining portion of the uterus, in addition to her ovaries and fallopian tubes, were normal in appearance, and the endometrial cavity was not breached. A thorough exploration of her abdomen and pelvis was performed and revealed no evidence of metastatic disease. Intraoperative pathologic review revealed necrotic tissue. Her postoperative course was unremarkable. Final pathological examination demonstrated high-grade ULMS within a histologically bland smooth-muscle neoplasm (Fig. 1(2C)). Varying degrees of cytologic atypia were observed, some areas demonstrated fascicles of bland appearing spindle cells, others contained a more cellular spindle cell component with minimal cytological atypia and 6 MF per 10 HPF, while other areas demonstrated sheets of spindle to ovoid cells with enlarged hyperchromatic nuclei and greater than 14 MF per 10 HPF. Myometrial invasion was present. The tumor showed slight alteration in immunoprofile with only focal desmin, smooth muscle actin, h-caldesmon, and PR staining as opposed to the diffuse staining for these uterine smooth muscle tumors in the previous myomectomy specimen. The loss of ER and presence of focal cytokeratin immunoreactivity showed slight aberration in immunoprofile with malignant transformation of the neoplasm. Again numerous immunostains including HMB-45, Melan A, SOX 10, CD34, and ALK1

were negative, excluding possibility of PEComa, melanoma, and gastrointestinal stromal tumor. Multiple institutions subsequently reviewed the patient's initial pathology materials in consultation and concurred with the initial diagnosis of benign leiomyoma. Cytological evaluation of ascites continued to be negative for malignancy.

CT and MRI scans of the chest, abdomen, pelvis, and brain showed no evidence disease one month post-operatively prior to the initiation of adjuvant chemotherapy and radiation (Fig. 1(3A)). She was treated per pediatric soft tissue sarcoma protocol ARST0332, using adjuvant chemotherapy and radiation. Chemotherapy included ifosfamide  $9 \text{ g/m}^2$  administered over 3 days and doxorubicin  $75 \text{ mg/m}^2$  over 2 days; with a cumulative anthracycline dose through treatment of  $375 \text{ mg/m}^2$ . Radiation therapy consisted of 4500 cGy over 25 fractions via volumetric modulated arc therapy (VMAT) to the pelvis followed by a robotic assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (Fig. 1(3B)). Final pathologic review of her uterus, cervix, and ovaries revealed no residual ULMS (Fig. 1(3C)). The patient's post-operative course was uncomplicated. She received three additional cycles of consolidation chemotherapy, also with ifosfamide and doxorubicin, the anthracycline was held during radiation per standard of practice.

Approximately four months after completion of adjuvant chemotherapy, she presented to the ER with mild abdominal pain and constipation. MRI of the abdomen and pelvis revealed three new abdominal masses measuring  $4.5 \times 3.7$  cm within the left lateral abdomen,  $2.4 \times 2.0$  cm within the left lower quadrant, and 0.9 cm posterior to the right hepatic lobe (Fig. 1(4A)). The patient underwent an exploratory laparotomy with tumor resection, small bowel resection, and omentectomy with surgical oncology. Tumors were located within the greater omentum, near the splenic flexure of the colon, and within the right retrohepatic space. All three tumors were completely resected and the patient underwent heated intraperitoneal chemotherapy (HIPEC) with cisplatin 84 mg and doxorubicin 25 mg at 42 degrees Celsius over one hour. The resected tumors were confirmed to be ULMS (Fig. 1(4B)) and submitted for Foundation Medicine for PD-L1 immunohistochemistry analysis (Dako 22C3 pharmDx™) with 0% tumor portion score. FoundationOne™CDx showing microsatellite-stable, low tumor mutational burden-low (0 Muts/Mb), and BRAF KIAA1549-BRAF fusion (chromosome location 7q34). The patient tolerated surgery well and is currently receiving gemcitabine and docetaxel.

### 3. Discussion

This case represents a high grade ULMS within a prior myomectomy site in a 16-year old female. This ULMS had many high-risk features including a large size, necrosis, high pathologic grade, myometrial invasion. The karyotypic aberrations including those of chromosomes 7,



12 and 14 and t(7;13)(p11.2; q11.2) noted in this LM has been previously described (Pandis et al., 1991). There was an unbalanced translocation between the long arms of chromosomes 12 and 14 [resulting in dup (12q)], and a derivative chromosome 15 with interstitial deletion and paracentric inversion of the long arm. Additionally, there was a balanced translocation between the short arm of chromosome 7 and the long arm of chromosome 13. Although the translocation t(7;13)(p11.2; q11.2) is unusual. Chromosomal alterations can be seen in most uterine leiomyomas but to a much lesser degree than in leiomyosarcomas. The presence of the numerous karyotype alterations in this case likely relate to the propensity of the histologically benign leiomyoma to have progressed into a malignant leiomyosarcoma.

Management of ULMS remains controversial. Following hysterectomy, the role of oophorectomy and lymph node sampling for stage I ULMS is unclear (Leitao et al., 2003). The GOG-277 international randomized phase III trial of adjuvant chemotherapy (ACT) versus no ACT in stage I ULMS closed due to low accrual and the results of their exploratory analysis indicated a weak signal for ACT (Hensley et al., 2018). In EORTC 55874 adjuvant pelvic radiation did not improve local recurrence rates or overall survival in uterine sarcomas, including ULMS (Reed et al., 2008). While there is no overall survival benefit from utilizing radiation therapy for stage I ULMS, this tumor was ruptured at the time of initial resection and the entire pelvis was at risk for disease recurrence. Given the risk of recurrence from the tumor spill, a multi-modality adjuvant approach was used. The available multi-modality regimens including ifosfamide and doxorubicin with 25 cycles of VMAT were utilized per the pediatric soft tissue sarcoma protocol (ARST0332). At relapse, she received surgery with cisplatin and doxorubicin HIPEC and receiving gemcitabine and docetaxel, all in a salvage attempt. Surgery with HIPEC has shown potential benefit in uterine sarcomatosis in recent small studies, though further validation in this area is warranted (Diaz-Montes et al., 2018). NCCN guidelines recognize ifosfamide and doxorubicin, gemcitabine and docetaxel, and several other combinations as viable treatment options. Pazopanib and trabectedin remain options for recurrent or refractory ULMS. The BRAF fusion identified in the recurrent tumor sample (KIAA1549-BRAF fusion) has five FDA approved therapies with clinical benefit in other tumor types (Binimetinib, Cobimetinib, Regorafenib, Sorafenib, and Trametinib) with ten clinical trials.

To our knowledge, this case represents the youngest patient diagnosed with a ULMS to date. Due to our patient's young age, a multi-disciplinary team was created, consisting of gynecologic oncology, pediatric radiation oncology, pediatric medical oncology, pediatric surgery, surgical oncology, child life and social work, and other supportive teams. To date, our patient's first round of chemotherapy was well tolerated with manageable side effects, including expected cytopenias requiring blood product support, neuropathic vulvar pain, moderate weight loss, and early menopause. After relapse, while receiving gemcitabine and docetaxel, our patient's clinical course has been complicated by E.coli septicemia and peripheral neuropathies. The patient is alive at the time of publication and deciding to continue chemotherapy or transition to a MEK inhibitor.

#### 4. Conclusion

In conclusion, malignant transformation of a leiomyoma to a ULMS is rare. We report a unique case of ULMS in an area of prior leiomyoma resection with high-risk features and subsequent rapid tumor recurrence despite aggressive adjuvant treatment. Owing to the extreme rarity of ULMS cases in the adolescent population, there is no well-established guidance on recommended treatment. Additional research is needed to study the molecular characteristics of this rare disease in adolescents compared with older patients to identify novel therapeutic strategies involving molecular targeting agents and immune checkpoint inhibitors alone and in combination with cytotoxic chemotherapy and radiation to achieve optimal outcomes.

#### Author contribution

All authors contributed to the literature search. JV and PK drafted the manuscript. SM performed the pathologic evaluation and provided the pathologic figures and legends. NP and LB provided input regarding chosen adjuvant therapy. KD, TC, UR, and LM provided review of manuscript and figures. KZ and RG revised the manuscript. All authors critically reviewed, edited, and approved the final manuscript for publication.

#### Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review upon request.

#### Financial disclosure

The authors have no conflicts of interest to disclose.

#### Disclaimer

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#### Declaration of Competing Interest

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