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Case report

Recurrent uterine inflammatory myofibroblastic tumor previously managed as leiomyosarcoma has sustained response to alectinib

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ABSTRACT

Soft tissue sarcomas encompass a wide range of histologic subtypes with varied clinical implications. The incorporation of comprehensive genetic profiling into clinical practice is refining our ability to make these distinctions in diagnosis to better reflect prognosis and clinical behavior of a tumor. In this report, we describe a case of recurrent inflammatory myofibroblastic tumor (IMT) of the uterus, initially diagnosed and managed as leiomyosarcoma. At the time of recurrence, the patient was found to have a *TNS1-ALK* rearrangement and was treated successfully with alectinib, a second-generation anaplastic lymphoma kinase (ALK)-inhibitor. She had a complete response by imaging six months after initiation of alectinib and remains without evidence of disease at 36 months follow-up. Pathology review in the setting of her known *ALK* fusion and the 2020 update to the World Health Organization Classification of Female Genital Tumors led to a change in diagnosis from leiomyosarcoma to IMT. Our case highlights the role of molecular testing in the diagnosis and management of uterine mesenchymal tumors and the efficacy of alectinib in this *ALK*-rearranged recurrent IMT of the uterus. Care must be taken to differentiate between IMT and other uterine mesenchymal tumors as this distinction can impact prognosis and management. Furthermore, this case adds to the growing body of evidence supporting the paradigm shift toward developing molecularly targeted therapies rather than disease site-specific treatments, especially in cases of recurrence as recommended by the National Comprehensive Cancer Network.

1. Introduction

Previously, nearly all uterine sarcomas were thought to represent leiomyosarcoma, low-grade endometrial stromal sarcoma, undifferentiated sarcoma, or ‘heterologous’ sarcomas such as rhabdomyosarcoma (Abu-Rustum, 2022; Fletcher, 2021). In recent years, additional histologic subtypes have been described and were recognized in the 5th edition of World Health Organization (WHO) Classification of Female Genital Tumors published in 2020. A major feature of the updated classification compared to the prior edition is a greater emphasis on key molecular events with integration of morphological and molecular features of tumors into the diagnostic criteria (WHO Classification of Tumors Editorial Board, 2020; McCluggage et al., 2020).

Among the newly detailed tumor types is inflammatory

myofibroblastic tumor (IMT), which has been a long-underdiagnosed entity. IMTs can be found in a wide range of anatomic locations with 75 % occurring in the abdominal cavity, particularly in the mesentery, greater omentum, and retroperitoneal space with remaining sites comprising of the areas of the head and neck, lungs, urinary bladder, central nervous system, and the female genital tract (Siemion et al., 2022). Following excision, approximately 10–25 % of patients develop local recurrence and < 5 % demonstrate metastatic disease. Histologically, these tumors are variably cellular, composed of myofibroblastic and fibroblastic spindle cells with loose myxoid, fascicular/compact or hyalinized growth patterns, variable (usually mild) cytologic atypia and mitotic rate, and accompanied by a prominent lymphoplasmacytic infiltrate (Fletcher, 2021).

Most IMTs overexpress anaplastic lymphoma kinase (ALK) protein by

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immunohistochemistry and are associated with *ALK* gene fusions (Abu-Rustum, 2022; McCluggage et al., 2020; Davare and Tognon, 2015). *ALK* is a receptor tyrosine kinase located on chromosome 2p23 which is involved in cellular growth (Davare and Tognon, 2015). *ALK* gene alterations can generate *ALK* fusion proteins which retain the *ALK* kinase domain sequence and become constitutively activated. *ALK* fusion proteins have been well-established in non-small cell lung cancer (NSCLC) (Davis et al., 2019). Approximately 50–60 % of IMTs harbor *ALK*-gene rearrangements compared to 2.4 % of reported leiomyosarcomas (Siemion et al., 2022; Davis et al., 2019). Reported gene fusions involved in IMT include *TPM3-ALK*, *TPM4-ALK*, *CLTC-ALK*, *RANBP2-ALK*, *CARS-ALK*, *ATIC-ALK*, *ETV6-NTRK3*, and *TFG-ROS1* (Agulnik et al., 2022). Since the increased recognition of IMT, the National Comprehensive Cancer Network (NCCN) Guidelines for Soft Tissue Sarcomas recommend *ALK*-inhibitors as first line treatment of IMT with *ALK* fusions citing crizotinib, ceritinib, brigatinib, and lorlatinib for this indication (Agulnik et al., 2022). Alectinib (ALECENSA), a second generation *ALK*-inhibitor, is not listed in the guidelines for treatment of IMT but is one of several *ALK*-inhibitors that has been FDA-approved and is established as standard of care for patients with *ALK* fusion positive lung cancers along with crizotinib, lorlatinib and ceritinib (Davis et al., 2019).

Here, we present a case of uterine IMT that recurred with local pelvic and pulmonary metastatic disease. The patient was initially diagnosed with a uterine leiomyosarcoma and after recurring, progressed on multiple lines of chemotherapy. Tumor genomic profiling was performed on the original tumor and a *TNS1-ALK* rearrangement was detected, which ultimately prompted a pathology re-review of the original resection specimen and subsequently the diagnosis was revised to malignant IMT. She was started on alectinib, and subsequent imaging showed a robust response with regression of her tumor and a sustained remission of over 36 months.

2. Case

The patient was a 71-year-old postmenopausal woman who presented to her primary care physician's office for pelvic pain and pressure. Transvaginal ultrasound revealed a presumed uterine leiomyoma measuring 19.5 × 12.3 × 9.8 cm. Magnetic resonance imaging (MRI) of the abdomen and pelvis confirmed a large 13 cm heterogeneous uterine mass with ill-defined margins suspicious for leiomyosarcoma (Fig. 1).

No definite extension was noted beyond the uterine wall; however, the mass abutted the pelvic sidewalls and iliac vasculature with small collaterals within the pelvis and anterior abdomen. No pelvic or inguinal lymphadenopathy was seen. Computed tomography (CT) scan of the chest revealed no evidence of metastatic disease. She denied a history of postmenopausal bleeding, and a preoperative endometrial biopsy was not performed. She underwent an exploratory laparotomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy. Intraoperative consultation on the uterine mass was interpreted as an atypical smooth muscle tumor. Final pathology was reported as leiomyosarcoma measuring 11.7 cm in greatest dimension with lymphovascular space invasion. The margins were free of tumor. Final pathology was consistent with stage 1B uterine leiomyosarcoma.

Postoperatively, the patient completed four cycles of adjuvant gemcitabine and docetaxel per the NCCN guidelines for management of leiomyosarcoma. Three years after completion of chemotherapy she was diagnosed with recurrent disease following a positron emission tomography (PET)-CT revealing hypermetabolic soft tissue lesions in the pelvic surgical bed and pulmonary nodules. Biopsy of the pelvic mass was reported as recurrent leiomyosarcoma. She was treated with six cycles of olaratumab (a PDGFR- α blocker) and doxorubicin. She initially had stable disease on treatment; however, repeat CT scan three months after completion of treatment showed progression of soft tissue implants in the pelvis (Fig. 2a and b).

Tumor genomic profiling was performed on her recurrent pelvic tumor biopsy which showed *TNS1-ALK* rearrangement, *CDKN2A/B* loss,

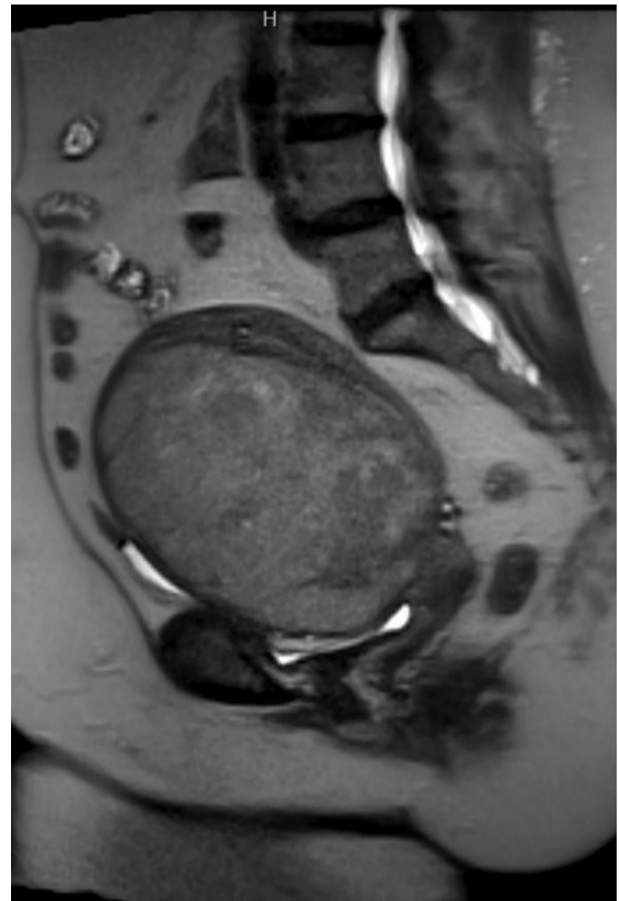


Fig. 1. Preoperative MRI, showing Large 13 cm heterogeneous uterine mass with ill-defined margins, suspicious for leiomyosarcoma. No pelvic or inguinal lymphadenopathy.

low tumor mutational burden (3Muts/Mb), and lack of microsatellite instability. No FDA approved therapies or clinical trials were identified for *CDKN2A/B* loss; however, *ALK*-inhibitors were identified treatment options in non-small cell lung cancer (NSCLC). After consultation with pharmacy and with an understanding that this was not a standard treatment for uterine leiomyosarcoma, she was started on alectinib. Repeat PET-CT ten weeks after starting treatment showed interval decrease in size and avidity of the pulmonary nodules and soft tissue masses within the pelvis with no evidence of new metabolically active disease. Imaging six months after treatment initiation showed a complete response with no residual disease (Fig. 2c and d).

A review of the patient's initial pathology was performed following the latest 5th edition of WHO Classification of Female Genital Tumors, and in the context of her molecular testing showing an *ALK* fusion. The diagnosis was changed from leiomyosarcoma to IMT (Fig. 3).

The patient has remained on alectinib for a total of 36 months, which she has tolerated well. Her surveillance imaging has showed no evidence of recurrent disease through the time of this report.

3. Discussion

Advancements in genomic sequencing have allowed the discovery of novel oncogenic drivers and subsequent targeted therapies across multiple cancer types, markedly impacting treatment options and patient outcomes (Xia et al., 2021). Since the incorporation of tumor molecular testing and the latest edition of WHO Classification of Female Genital Tumors from 2020, uterine IMTs are being increasingly diagnosed and studied. Uterine sarcomas are uncommon neoplasms that account for 2–4 % of uterine malignancies. While leiomyosarcomas comprise 70 %

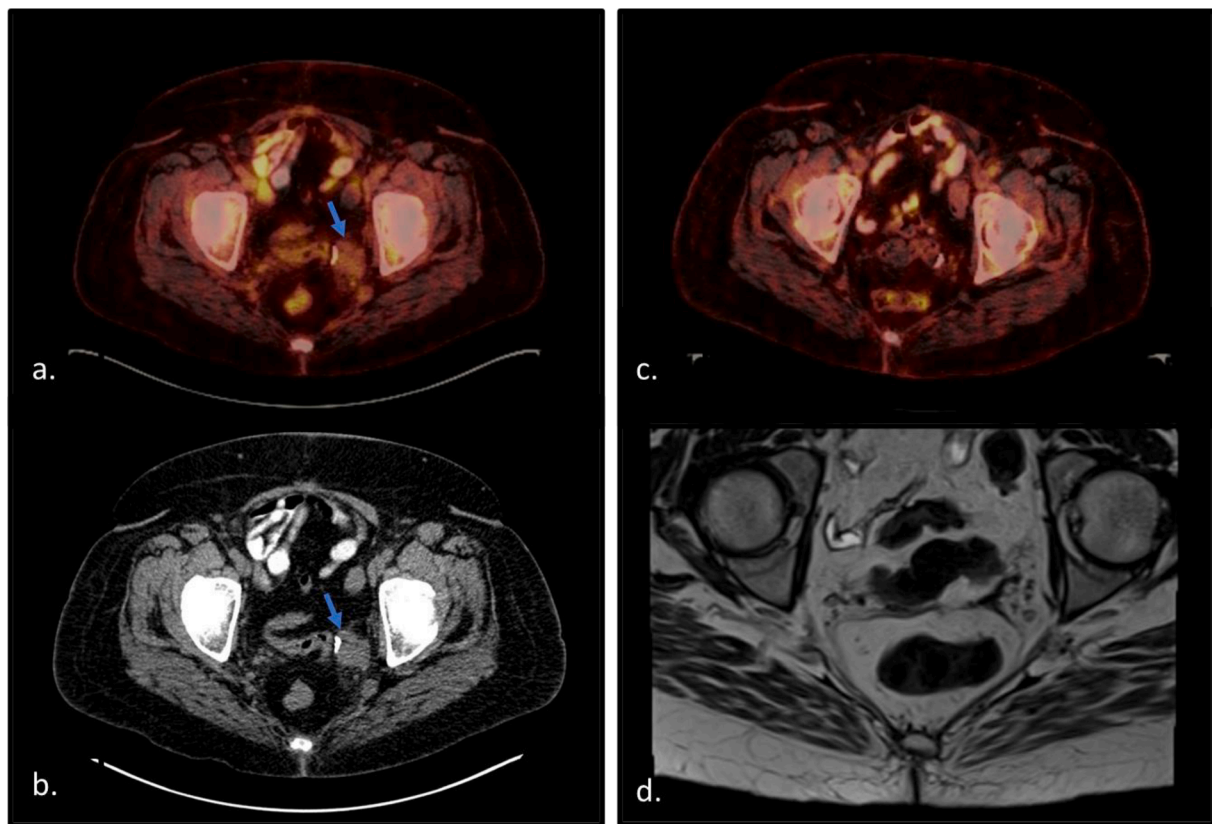


Fig. 2. PET CT and MRI imaging demonstrating recurrence and disease response to alectinib. a) PET CT showing FDG avid pelvic soft tissue lesion of biopsy proven recurrence (SUV 3.1). b) CT showing the $3.2 \times 3 \times 2.3$ cm mass increased in size following second-line therapy for leiomyosarcoma. Additional soft tissue nodules were seen in at the vaginal cuff and in the right middle lobe of the lung and mediastinum, not pictured here. c) PET-CT showing disease response to alectinib. d) Given low FDG avidity of biopsy proven recurrence, MRI was recommended for best assessment of residual disease. MRI six months after initiation alectinib was without evidence of disease.

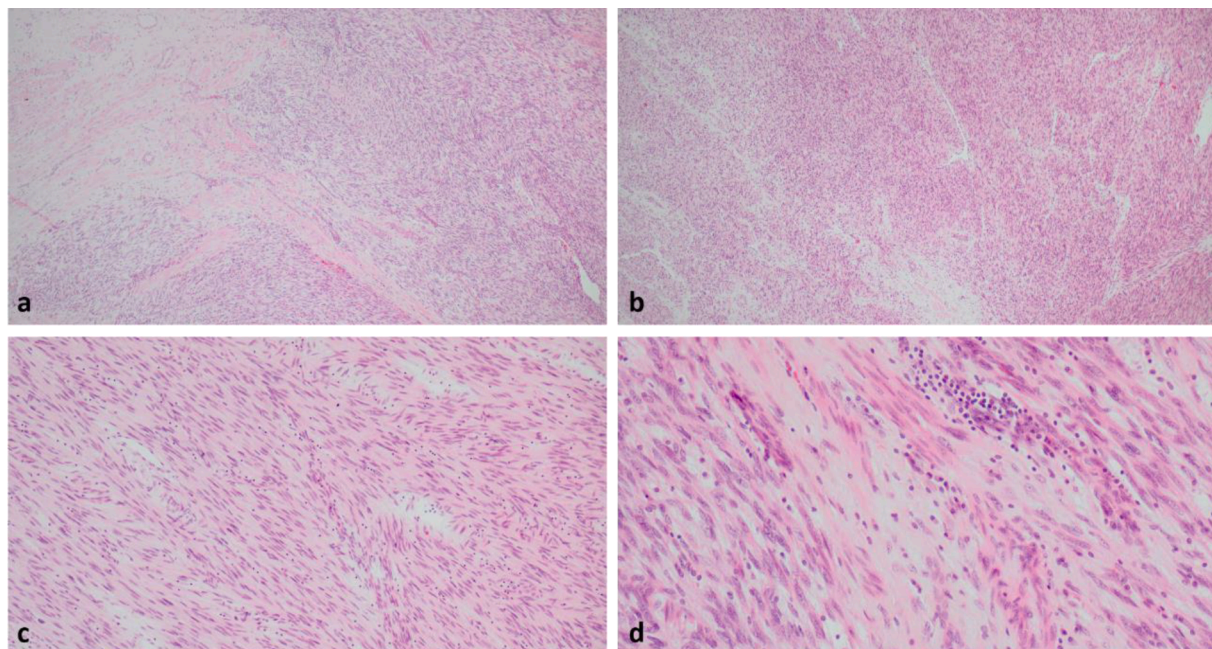


Fig. 3. Pathology. Uterine IMT with focally infiltrative borders (a), composed of intersecting fascicles of spindle cells (b) with moderate cytologic atypia, associated with lymphoplasmacytic infiltrate (d). Myxoid change is not conspicuous. Hematoxylin-eosin stain; original magnification: x100 (a, b), x200 (c, d).

of all malignant mesenchymal tumors of the uterus, they remain rare with an overall incidence of 0.4–0.9 in 100,000 women (Mas et al., 2019). The overall incidence of uterine IMT is not well established, although it is likely underdiagnosed due to being mistaken for other more common benign and malignant tumors including leiomyoma, leiomyosarcoma, and endometrial stromal sarcoma (Shukla and Mittal, 2019; Hensley et al., 2020). IMTs are most commonly benign but have a potential for extrauterine spread and/or recurrence. In a study of 23 cases of IMT, only 4 behaved in a malignant fashion as determined by the presence of extrauterine disease at diagnosis and/or recurrence (Bennett et al., 2020).

Several cases have been described where a previous diagnosis was revised after discovering an *ALK* fusion on molecular testing (Hensley et al., 2020; Kyi et al., 2021; Lee et al., 2019; Zhang et al., 2020; Testa et al., 2021). On review of the literature, this is the third reported case of uterine IMT with an aggressive clinical behavior containing a *TNS1-ALK* fusion specifically (Kyi et al., 2021; Lee et al., 2019). This is the second such case treated with alectinib. In 2021, Kyi et al described a case of uterine IMT containing *TNS1-ALK* fusion that was treated with alectinib as second line therapy for 12 months prior to disease progression (Kyi et al., 2021). There are also limited reports of leiomyosarcomas containing *ALK* fusions, but it cannot be discerned from the published manuscripts if IMT was considered in the differential diagnosis (Davis et al., 2019; Ross et al., 2017). Of note, fascicular areas in uterine IMTs tend to be more cellular and often have less prominent inflammation compared with myxoid areas. Therefore, IMTs exhibiting a fascicular growth pattern exclusively or predominantly appear to closely resemble and mimic a smooth muscle neoplasm, as demonstrated in our case.

The distinction between leiomyosarcoma and IMT is meaningful in treatment planning. The preferred first-line systemic therapies for leiomyosarcoma include doxorubicin and gemcitabine/docetaxel, still reporting a high recurrence rate of approximately 50–70 % (Abu-Rustum, 2022). If a tumor is determined to be an IMT, these cytotoxic regimens are not recommended in the upfront setting or as first line in the recurrent setting when *ALK* fusions are present (Agulnik et al., 2022). Regardless of diagnosis, the presence of an *ALK* fusion provides an opportunity for a targeted treatment option with demonstrated clinical activity (Kyi et al., 2021; Testa et al., 2021; McKeage, 2015). The NCCN Guidelines for Uterine Neoplasms now recommend comprehensive genomic profiling with a validated assays including at least NTRK, MSI, and TMB as it is informative for pathologic characterization and identifying rare pan-tumor targeted therapy opportunities (Abu-Rustum, 2022). The NCCN Guidelines for Soft Tissue Sarcomas recommends that *ALK* fusion-containing IMTs regardless of disease site are treated with *ALK*-inhibitors as previously listed, but not including alectinib (Agulnik et al., 2022).

Alectinib is an orally available second generation *ALK*-inhibitor with antineoplastic activity. It binds to and inhibits *ALK* kinase, *ALK* fusion proteins, and the gatekeeper mutation ALK1196M to disrupt *ALK*-mediated signaling with the overall function of inhibiting tumor cell growth in *ALK*-overexpressing tumor cells (Mok et al., 2020). Currently, it is used as first-line therapy for *ALK*-positive NSCLC with a 12-month event free survival rate of 68 % (Ross et al., 2017). To date, *ALK*-inhibitors are only FDA approved to treat NSCLC (Abu-Rustum, 2022). The ALEX trial is a recent international, randomized, open-labeled phase 3 trial in which alectinib was compared to crizotinib, the previous standard of care *ALK*-inhibitor in patients with untreated, advanced *ALK*-positive NSCLC. They treated patients until disease progression, toxicity, withdrawal, or death reporting a median treatment duration of 28.1 months with alectinib compared to 10.8 months²¹. Common side effects include fatigue, hematuria, cough, joint pain and swelling. Toxicities requiring discontinuation include hemolytic anemia, symptomatic bradycardia, interstitial lung disease and CPK elevation greater than five times the upper limit of normal. Extrapolating from lung cancer data in the absence of studies regarding alectinib in uterine IMTs, we intend

to continue treatment until the patient progresses or has toxicity with reassessment at the five-year mark. To date, she does not report any toxicities.

Our case highlights the role of molecular testing in the diagnosis and management of uterine mesenchymal tumors and the efficacy of alectinib in this *ALK*-rearranged recurrent IMT of the uterus. Clinicians need to be aware of this entity in the differential as it can impact prognosis and treatment planning. Furthermore, this case adds to the growing body of evidence supporting the paradigm shift toward developing molecularly targeted therapies based on individual tumor characteristics rather than solely relying on histology and disease site-specific treatments.

Informed 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 by the Editor-in-Chief of this journal on request.

CRedit authorship contribution statement

Erica V. Carballo: Writing – original draft. **Tra V. Pham:** Writing – review & editing. **Gulisa Turashvili:** Writing – review & editing. **Krisztina Hanley:** Writing – review & editing. **Kristen D. Starbuck:** Writing – review & editing, Supervision. **Jane L. Meisel:** Writing – review & editing, Conceptualization, Supervision.

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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