Larotrectinib in a Patient With Advanced Pleomorphic Liposarcoma of the Uterus

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ABSTRACT

Pleomorphic liposarcoma of the uterus (PLU) is an extremely rare disease with poor prognosis. Limited treatment options exist for these patients, and disease recurrence usually occurs rapidly within months of initial diagnosis. Few case reports of metastatic PLU are available in the literature. We describe a 70-year-old woman who presented with a large uterus and ovarian mass on imaging and negative serum tumor markers and endometrial biopsy. Staging revealed localized disease. Surgical resection revealed PLU on pathology. Immunohistochemistry was negative for smooth muscle actin (SMA), S100, and MDM2, and positive for CD10 and cyclin-D1. She was treated with adjuvant therapy and experienced disease recurrence in the liver at 15 months from surgery. Genetic testing of the metastasis showed IQGAP-NTRK3 gene fusion. She was given entrectinib but continued to show progression in the liver. Right partial hepatectomy was performed, showing positivity for CD10, BCL-1, MDM2, and SMA on tumor staining. Treatment was switched to pazopanib with disease progression in the neck. She was treated with larotrectinib last, showing no disease progression and adequate tolerance of therapy after 18 months of this treatment. This is the first case in the literature of metastatic PLU with NTRK3 fusion treated with sequential first-generation NTRK inhibitors. More case reports are needed to identify commonalities and therapeutic options. Genetic testing in all PLU cases is needed for targeted therapy approaches.


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Soft tissue sarcomas are rare malignancies of mesenchymal origin, accounting for approximately 1% of adult cancers, and an estimated 13,500 new cases were diagnosed in 2019 in the United States.1 Soft tissue sarcomas constitute a heterogeneous and complex group of tumors comprising approximately 100 different histologic and molecular subtypes, with variable clinical behavior.2 Uterine adipocytic tumors account for only 0.03% to 0.2% of all uterine tumors.3 Liposarcomas constitute a subgroup of these adipocytic tumors. They can be classified further as dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma, or liposarcoma not otherwise specified.2 These tumors are likely to arise from malignant transformation of a benign mesenchymal tumor.4,5 Other theories explaining their origin include adipocytic differentiation of a progenitor connective tissue cell, misplacement of embryonic adipocytes, fatty infiltration by uterine soft tissue, and iatrogenic displacement.5 Pleomorphic liposarcoma of the uterus (PLU) is therefore an extremely rare disease. It is composed of smooth muscle, mature adipocytes, and lipoblasts.6 PLU presents most commonly in postmenopausal women and has a poor prognosis. Approximately 50% of the tumors display rapid progression after initial resection, and patients with PLU have an overall survival rate of 40% at 5 years.7,8 Tumor recurrence usually occurs within months of initial resection.9 Systemic treatment options available to patients with advanced disease are limited.10 The histologic phenotype of pleomorphic liposarcoma bears a certain semblance to undifferentiated pleomorphic sarcoma with unequivocal lipoblastic differentiation (characterized by the presence of lipoblasts). Not infrequently, it can acquire an epithelioid phenotype mimicking carcinoma (but with areas of lipoblastic differentiation), but by definition will lack expression for epithelial markers.5 The tropomyosin-related receptor kinase (Trk) family of proteins includes 3 transmembrane neurotrophin receptors TrkA (NTRK1), TrkB (NTRK2), and TrkC (NTRK3). They are encoded by NTRK genes (NTRK1, NTRK2, and NTRK3) located on human chromosomes 1q23.1, 9q21.33, and 15q25.3, respectively.11,12 Gene fusions involving NTRK1–3 genes lead to a constitutive activation or overexpression of Trk receptors, which can make them oncogenic.13 These fusions have been
appreciated in a variety of tumors types. Treatment of patients with cancer harboring these fusions using targeted Trk inhibitors, such as entrectinib or larotrectinib, demonstrated remarkable responses.14–19

When a patient is suspected of having liposarcoma, immunohistochemistry (IHC) and next-generation sequencing (NGS) are used to determine the specific tumor type, define prognosis, and determine genetic abnormalities, such as NTRK fusions, that can indicate potential treatment options.20 A minimal number of case reports are available in the literature describing PLU harboring an NTRK fusion. Hence, the importance of continued reporting of these rare cases in the literature.

Here we present a case report of metastatic PLU treated sequentially with NRTK inhibitors. To our knowledge, this is the first case reported in the medical literature.

Case Report

A 70-year-old woman presented to The Ohio State University–James Cancer Center as a transfer from an outside hospital for evaluation of a large uterine mass seen on CT of the abdomen/pelvis. She sought medical attention the previous day after experiencing sudden abdominal pain. CT of the abdomen/pelvis and transvaginal ultrasound showed an enlarged uterus and a 7.3 × 5 × 6.5 cm, thick-walled septated mass in the left ovary, concerning for malignancy (no image available). Serum tumor markers CA-125, CEA, and CA 19-9 were negative. Endometrial biopsy was negative for malignancy as well. The patient underwent an elective robotic hysterectomy and bilateral salpingo-oophorectomy 2 weeks later. Final pathology from the surgery revealed PLU with an anterior and posterior size of 7.0 × 6.0 × 2.1 cm and 8.0 × 6.5 × 4.0 cm, respectively. The histopathology was high-grade spindle cell sarcoma with associated pleomorphic lipoblasts, consistent with PLU. The immunophenotypic profile was nonspecific and neoplastic cells were focally positive for CD10 and cyclin-D1, and negative for estrogen receptor, progesterone receptor, HHF35, smooth muscle actin (SMA), H-caldesmon, HMB45, melan-A, desmin, S100, myogenin, myoglobin, MDM2, pancytokeatin-AE1/3, and epithelial membrane antigen. Her final pathologic staging was IB (T1bN0M0 grade 3 AJCC).

Given the aggressive nature of this tumor and high risk of recurrence, it was recommended that the patient receive adjuvant chemotherapy to decrease the risk of recurrence. She was treated with 6 cycles of doxorubicin and olaratumab with acceptable tolerance and continued olaratumab maintenance therapy after the initial 6 cycles.

Unfortunately, the patient was found to have metastatic disease in the liver 15 months after her initial surgery (Figure 1). The patient’s diagnostic liver tumor biopsy was tested using the FoundationOne Heme panel (Foundation Medicine). This multitarget comprehensive genomic profiling assay uses DNA and RNA sequencing of hundreds of cancer-related genes. In this patient’s case, it demonstrated the presence of IQGAP-NTRK3 fusion. The patient was then given entrectinib as part of a clinical trial (ClinicalTrials.gov identifier: NCT02568267). This trial was an open-label, multicenter, global phase II basket study of entrectinib treatment in patients with locally advanced or metastatic solid tumors harboring NTRK1/2/3, ROS1, or ALK gene rearrangements. The patient completed 4 cycles of this medication with acceptable tolerance.

Entrectinib was discontinued after 4 cycles because of disease progression in the liver (Figure 2). The patient underwent right partial hepatectomy of segments 6 and 7, excising a 4.5-cm and 2.5-cm mass from each segment, respectively. The pathology was consistent with metastatic PLU (Figure 3). The preponderance of the histopathologic

Figure 1. First liver metastases seen in (A) right posterior hepatic lobe measuring 1.9 cm and (B) right inferior lobe measuring 1.1 cm (yellow arrows) while patient received olaratumab maintenance therapy 15 months after initial surgery.
phenotype was that of undifferentiated pleomorphic spindle cell sarcoma. Lipoblasts were not identified in the metastatic tumor, but this is not uncommon in metastatic sites, and their absence does not negate the diagnosis, because the original tumor was diagnosed as such. Second, the immunophenotypic profile was similar to the primary PLU, with the neoplastic cells demonstrating positivity for CD10, cyclin-D1, and BCL-1 and negative for S100, CD117, desmin, AE1/AE3, and estrogen receptor, except for multifocal reactivity for SMA and rare weak staining for MDM2 (of unknown significance). In view of the nonspecific focal and weak staining for MDM2 by IHC, subsequent fluorescence in situ hybridization for MDM2 amplification was negative, excluding the possibility of a dedifferentiated liposarcoma. After surgery, the patient was started on pazopanib until disease progression was seen in the neck 3 months later (Figure 4), for which she received 36 Gy of conformal palliative radiation to the right side.

Following radiation, the patient experienced considerable pain in her neck and was given larotrectinib due to clinical concerns of disease progression, achieving stable disease with good tolerance. She required dose adjustment due to adverse effects (grade 2 ataxia and fatigue). At the time of writing this article, 18 months into this treatment, there has not been evidence of disease progression. Currently, it has been 4.1 years since the initial diagnosis.

**Discussion**

We present the case of a patient with metastatic PLU, which is a very rare disease. At the time of writing, our patient has had disease progression but experienced overall stability with the interventions described. She has remained without evidence of disease progression since beginning treatment with larotrectinib. This case report is, to our knowledge, the first in the literature describing the sequential use of NRTK inhibitors in metastatic PLU.

IHC and genetic testing are at the forefront of cancer studies to find targeted therapies for patients and better understand the disease. Schoolmeester et al. reported a case of pleomorphic liposarcoma with IHC positive for SMA, h-caldesmon, and desmin, although S100 was positive in some lipoblasts and mature adipocytes and MDM2...
was negative. Another report of a pleomorphic liposarcoma by Drilon et al\textsuperscript{14} showed positivity for SMA in the tumor sample. Our patient’s primary tumor was negative for these stains. Liver metastases then showed positivity for MDM2 and SMA. NGS of the tumor in the report by Schoolmeester et al\textsuperscript{10} found mutations in \textit{TP53}, \textit{FAT1}, and \textit{TERT}. Our sample had a \textit{TP53} mutation as well, and notably, an \textit{NTRK3} fusion found through foundation medicine testing. Taken together, the IHC and genetic testing comparisons between these case reports emphasize the fact that larger sample sizes are needed to find common markers or targets for these rare tumors that might affect treatment options and help determine prognosis.

Fusions involving \textit{NTRK3} are oncogenic drivers in a large number of mesenchymal tumors.\textsuperscript{2} Targeted therapy with an NTRK inhibitor such as larotrectinib has led to a positive response in a large number of patients with cancers that harbor \textit{NTRK1/2/3} fusions.\textsuperscript{6,7,21,22}

Our patient had an \textit{IQGAP-NTRK3} fusion. She experienced disease progression while receiving entrectinib, but has remained stable 18 months into treatment with larotrectinib. Given the limited therapeutic options available to these patients, NGS for targeted agents is fundamental, when possible, in patients with sarcomas.

Resistance to TRK inhibition by entrectinib and larotrectinib can occur through the development of \textit{NTRK} gene mutations in the solvent region of the kinase (eg, \textit{NTRK1} p. G595R and \textit{NTRK3} p. G623R) and in the xDFG motif (\textit{NTRK1} p. G667C) that in general create steric hindrance and prevent the binding of the compound to the kinase.\textsuperscript{23–25} This process is not completely understood and not straightforward, because in vitro kinase assays have shown that some of these mutants then increase affinity for ATP when compared with the wild-type kinase.\textsuperscript{23} Therefore, it is possible that our patient developed mutations that provided resistance to entrectinib but not necessarily resistance to larotrectinib, because acquired resistance is a process that depends on the selective pressure of the inhibitor.

Our case report shows that even though inhibitors are first generation, resistance to one does not always indicate resistance to the other. This subsequent response to larotrectinib strengthens the argument that NGS is a helpful tool and should be attempted if available at time of diagnosis, and also when patients develop resistance to the first inhibitor, in order to create a larger sample size and determine mutations that might predict response to another first-generation inhibitor even if steric hindrance is seen. The fact that our patient has been treated with 2 first-generation inhibitors without sustained resistance also adds to the novelty of this report.

New NTRK inhibitors such as selitrectinib (LOXO-195) and repotrectinib are second-generation TRK inhibitors currently being developed as newer therapeutic alternatives to overcome the observed NTRK resistance with first-generation inhibitors. These new inhibitors are designed to avoid steric hindrance from solvent front substitutions. There is a well-known case published of a patient with mammary analog secretory carcinoma who was found to have a solvent region mutation after developing resistance to entrectinib and subsequently did well on repotrectinib.\textsuperscript{26}

Conclusions

This clinical report proves the importance of continuing to expand treatment alternatives and reporting of fusion-driven sarcomas, as well as performing additional NGS when resistance to treatment develops.