Clinical Case Report

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Significant partial response of metastatic intra-abdominal and pelvic round cell liposarcoma to a small-molecule VEGFR-2 tyrosine kinase inhibitor apatinib

A case report

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Abstract

Introduction: Myxoid/round cell liposarcoma is the second most common subtype of liposarcoma. Chemotherapy and radiotherapy have a limited efficacy for treating advanced myxoid/round cell liposarcoma, with relatively serious side effects.

Case presentation: We herein present a 68-year-old Chinese woman initially diagnosed with advanced multiple intra-abdominal and pelvic round cell liposarcoma.

She refused to receive cytotoxic chemotherapy and received apatinib as the first-line therapy, a novel tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2 that has been used in the treatment of patients with metastatic gastric cancer who progressed with 2 or more chemotherapy regimens. This patient was partially responsive to apatinib with a dose of 500 mg daily. No serious drug-related side effects were observed.

Conclusion: Our findings indicate that some cases of liposarcoma may be responsive to antiangiogenic agent apatinib. Randomized clinical studies are needed to further confirm the efficacy and safety of apatinib in the clinical treatment of liposarcoma.

Abbreviations: ^{18}F-FDG = fluorodeoxyglucose, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, MRLS = myxoid/round cell liposarcomas, OS = overall survival, PET/CT = positron emission tomography/computed tomography, PFS = progression-free survival, STSs = soft tissue sarcomas, VEGFR-2 = vascular endothelial growth factor receptor-2, WHO = World Health Organization.

Keywords: apatinib, intra-abdominal, round cell liposarcoma, targeted therapy, tyrosine kinase inhibitor, VEGFR-2

1. Introduction

Soft tissue sarcomas (STSs) represent a rare and heterogeneous group of malignant tumors with mesenchymal origin that affect approximately 1% of all adult malignancies.[1] Liposarcomas appear to originate from precursors of adipocytes and are the most common type of malignant soft tissue sarcomas, representing at least 20% of all sarcomas in adults.[2] The four main morphologic subgroups are well-differentiated, dedifferentiated, myxoid/round cell, and pleomorphic liposarcomas.[3] There is a great range of biologic behavior amongst these subtypes. Myxoid/round cell liposarcoma (MRLS) is the second most common subtype of liposarcoma, accounting for 20% to 50% of all liposarcoma. Although World Health Organization (WHO) considers MRLS as a combined subtype, and myxoid and round cell liposarcoma variants share the same reciprocal translocation t(12;16)(q13;p11), round cell liposarcomas are considered high grade and were more likely to metastasize to extrapulmonary organs, most commonly the abdomen, than well-differentiated and myxoid liposarcomas.[4,5] Most liposarcomas are initially found in the lower extremities and retroperitoneum, whereas primary intra-abdominal and pelvic liposarcomas are considered as uncommon events. Bowel obstruction, bleeding, and perforation can be usually generated by intra-abdominal invasion of liposarcoma.[1]

Surgical resection is the only potentially curative treatment for localized liposarcomas. However, most patients receiving surgery will ultimately relapse or metastasize, and some patients are unresectable because of metastatic, extensive involvement, or the presence of multiple peritoneal implants at the time of initial diagnosis.[5] Although radiotherapy and cytotoxic chemotherapy have been used for clinical management of metastatic or

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unresectable liposarcomas, the efficacy with regular treatment for advanced liposarcomas is limited, and most cases received best supportive care only.

Apatinib (Hengrui Pharmaceutical Co. Ltd, Shanghai, China), an orally bioavailable small-molecule tyrosine kinase inhibitor selectively targeting vascular endothelial growth factor receptor-2 (VEGFR-2), has a survival benefit for patients with advanced gastric cancer in phase II and III trials.[6,7] In 2014, apatinib was approved by China State Food and Drug Administration for the treatment of patients with metastatic gastric cancer who received two or more lines of prior chemotherapy. Given its potent inhibition of VEGFR-2 signaling pathway, this antiangiogenic agent also shows wide potential efficacy in a variety of solid tumors including metastatic lung, colon, and breast cancer.[8,9] We herein report a case of round cell liposarcoma in which apatinib produced an excellent tumor response, without serious treatment-associated side effects.

2. Case presentation

In September 2015, a 68-year-old Chinese woman visited our hospital with a 6-month history of upper abdominal fullness sensation and weight loss, and with 1-month abdominal masses, but there was not direct pain associated with the masses. Physical examinations showed a distended abdomen with multiple, non-tender, and immobile abdominal masses, without any signs of peritonitis. Abdominal ultrasonography showed multiple masses containing cystic and solid components, with a giant one measuring $20 \times 14 \times 9$ cm that located in the left abdomen. A computed tomography (CT) scan demonstrated extensive soft tissue mass lesions with heterogeneous density in abdominal and pelvic locations (Fig. 1). The masses were extended to small intestine, uterus, and bladder. Positron emission tomography/computed tomography (PET/CT) scan revealed high fluorodeoxyglucose (^{18}F-FDG) uptake up to SUV_{max} 12.1 for most hypermetabolic abdominal and pelvic masses, with a metastatic lesion in the liver (Fig. 2).

This patient had an Eastern Cooperative Oncology Group (ECOG) score of 2. Laboratory testing, including blood routine, biochemical, and urinalysis, revealed some abnormal results (hemoglobin: 102 g/L; albumin: 29.1 g/L; bile acid: 21.0 μmol/L). Fine-needle aspiration for the mass with maximum size was taken, and pathological report revealed the diagnosis of a round cell liposarcoma with immunohistochemistry results: vimentin (+), P504S (+), S-100 (partly +), CK (−), p16 (−), and EMA (partly +). At immunohistochemistry, the section showed positive staining for CD31 and CD34, and strong expression of VEGFR-2 protein in tumor cells (Fig. 3).

This patient did not receive surgery interaction and radiotherapy because of extensive lesions and metastasis to the liver. She refused to receive thermotherapy. After providing written and informed consent, this patient was administrated with apatinib (500 mg daily) on October 12, 2015. After nearly 1 month of treatment with apatinib, the upper abdominal fullness sensation and weight loss were relieved significantly. The size of abdominal and pelvic masses was significantly decreased. The middle and right abdominal mass approximately diminished, and the metastatic lesion in the liver remained stable (Fig. 1). The latest follow-up with CT scan was conducted on April 15, 2016. The patient is still alive without progression. Overall, this patient got a partial response to apatinib treatment. In addition, the levels of hemoglobin and albumin were within their normal ranges.

Treatment-related side effects were monitored weekly during apatinib treatment. The side effects included hematologic and nonhematologic toxicities. Hypertension (grade 2) and elevated transaminase (grade 1) were mainly nonhematologic toxicities. Thrombocytopenia (grade 2) was found at the third week of

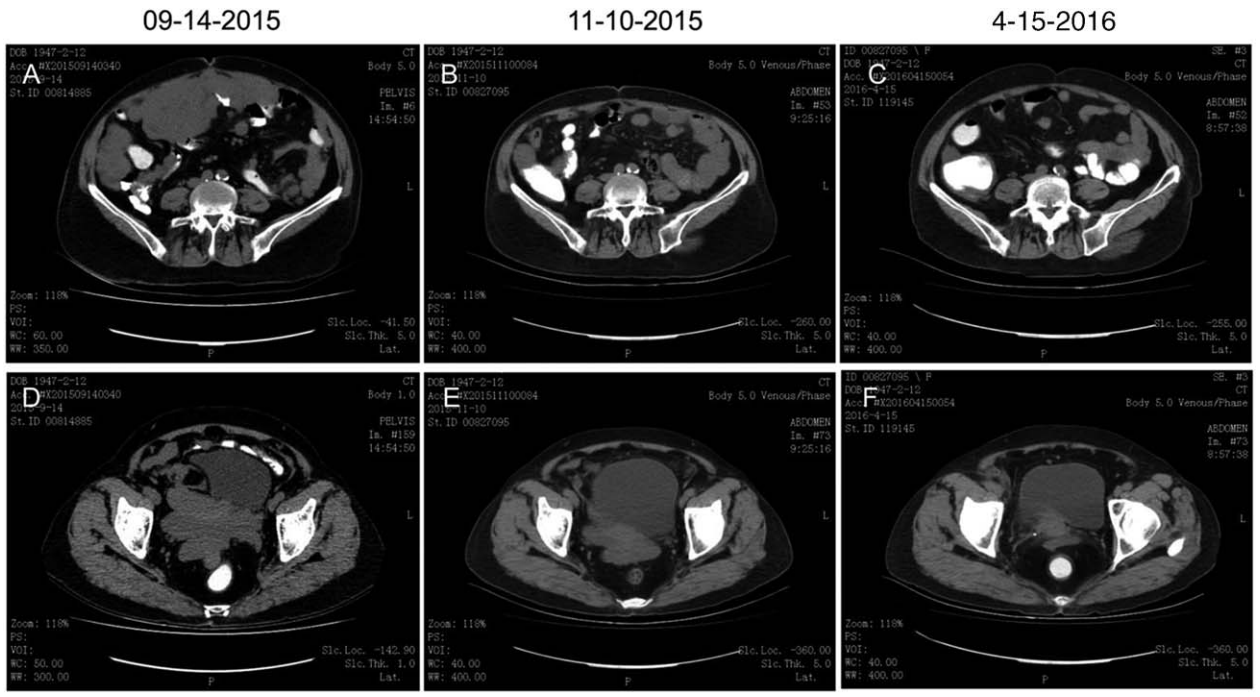

Figure 1. A computed tomography scan showed coexisting abdominal and pelvic masses (A and D) at the time of initial diagnosis. The size of mass lesions in abdominal and pelvic locations decreased significantly following treatment with apatinib of 500 mg daily (B, C, E, and F).

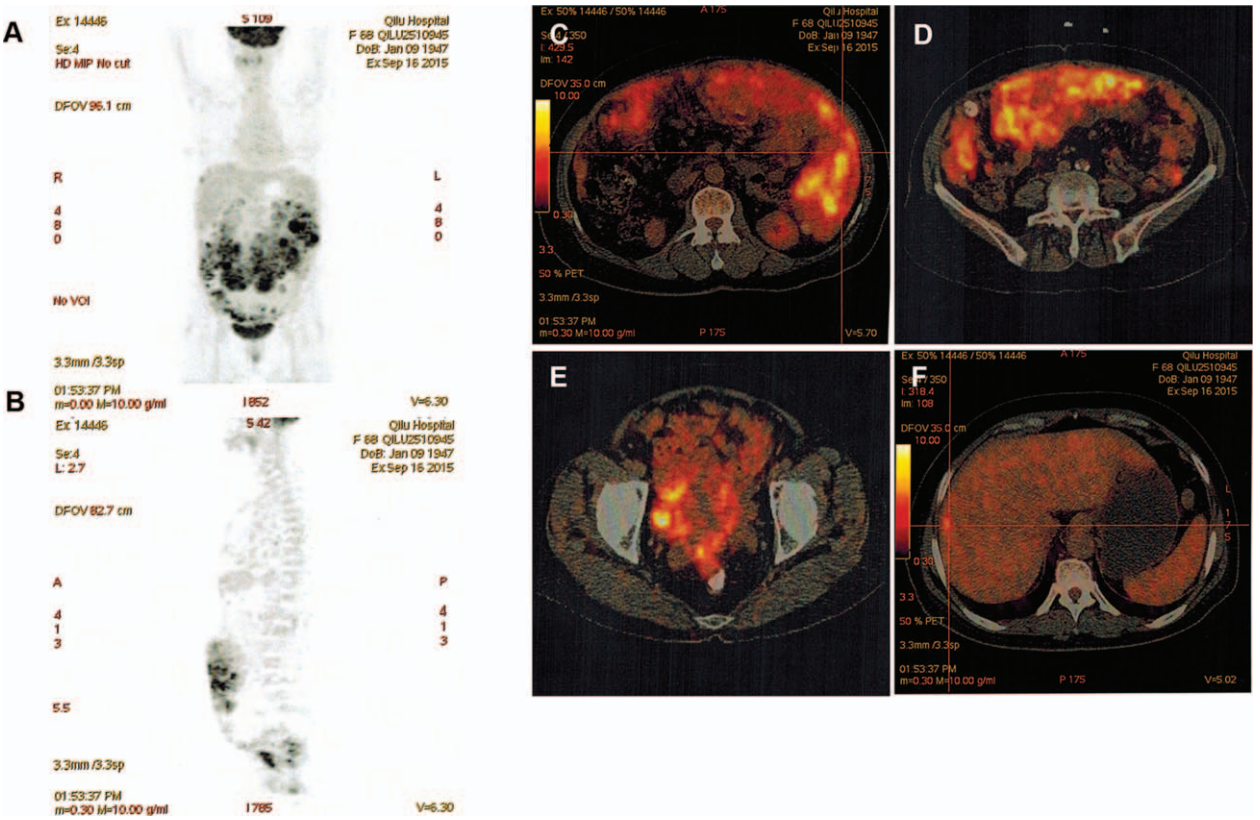

Figure 2. Maximum intensity projection images (A and B) and positron emission tomography/computed tomography fusion images (C, D, E, and F) show heterogeneous fluorodeoxyglucose (FDG) uptake in multiple abdominal and pelvic masses. Maximum standardized uptake value (SUV_{max}) of the masses is 12.1.

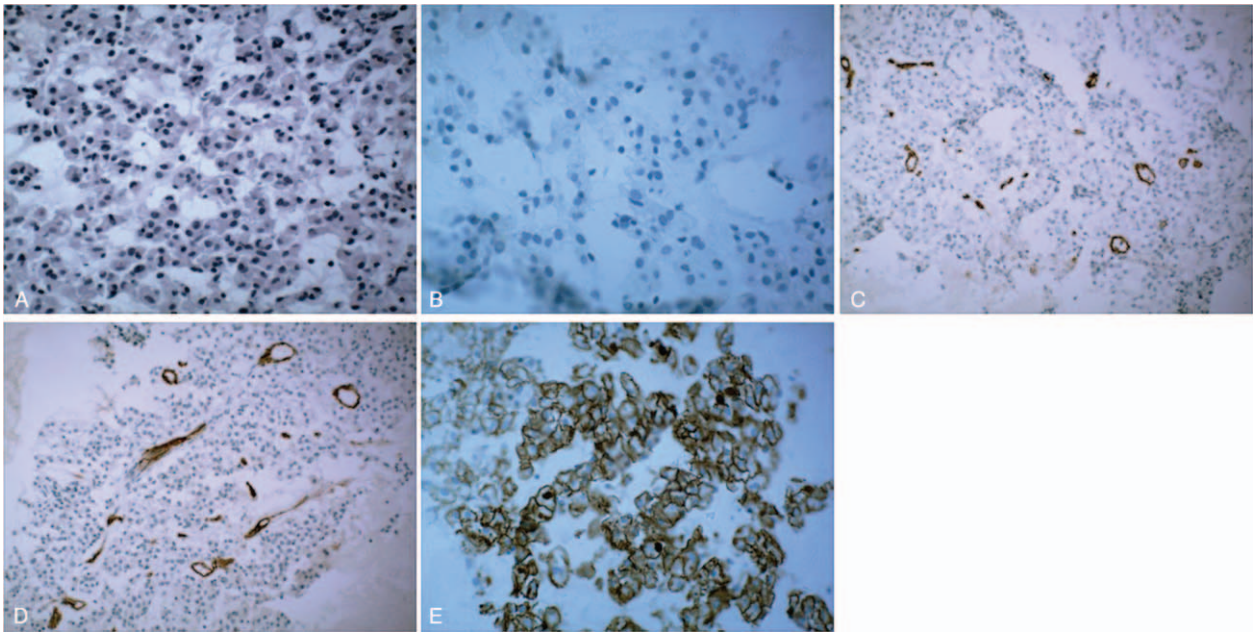

Figure 3. The patient was initially diagnosed with myxoid/round cell liposarcoma by fine-needle aspiration. (A) Hematoxylin and eosin stain (400× magnification). The section showed negative staining for p16 (B), positive staining for CD31 (C) and CD34 (D) and a large number of immature and intermediate blood vessels were found in the tumor area. (E) A strong positive staining for VEGFR-2 was also found in most cancer cells (immunostaining, 200× magnification).

apatinib treatment. Hypertension was controlled well by administration with antihypertensive drugs. No grade 3 to 4 side effects and other treatment-associated toxicities such as proteinuria and hand–foot syndrome were observed. This patient did not have tumor lysis syndrome. She continued to receive apatinib at a maintenance dose of 500 mg daily and tolerated well without serious side effects.

3. Discussion

Liposarcomas are the most common subtype of all soft tissue sarcomas. Although liposarcomas may arise in any region of body that contains fat, coexisting primary intra-abdominal and pelvic liposarcomas are uncommon.[5] Round cell liposarcoma variant is regarded as a histologic progression of pure myxoid liposarcoma to hypercellular round cell morphology (>5% round cell phenotype). Myxoid liposarcomas with a round cell component may behave aggressively.[3] Surgery resection is the standard of care for MRLS patients with localized disease, but complete surgical resection is achieved in less than 70% of these patients due to close proximity to vital organs. About 25% of patients will develop metastatic distant disease after successful treatment of their primary tumor. Patients with giant round cell liposarcoma (tumors >10 cm) have a high risk of recurrence and metastasis, especially in extrapulmonary locations.[5]

On the other hand, metastatic MRLS are related to more poor survival compared with localized disease. Surgical interventions seem to be associated with improved disease-specific survival.[10] Although surgery is offered as standard treatment, the decision-making should be multidisciplinary and be made on a case by case basis, especially for metachronous resectable lung metastasis without extrapulmonary spread.[11] In addition, chemotherapy remains the standard treatment for extrapulmonary metastatic disease. In highly selected individual cases, surgery may be considered as an option, taking into consideration tumor locations, the underlying histology of the tumor, the natural history of the disease, and expected responsiveness to systemic therapy.[12] Palliative chemotherapy with or without radiotherapy are usually reserved for other advanced MRLS, with an improved progression-free survival (PFS). Recent report showed that helical tomotherapy-based intraperitoneal radiotherapy might be a new option of salvage treatment for patients with liposarcoma with multiple peritoneal seeding.[13]

Understanding of the distinct subgroup of soft tissue sarcoma helps develop and introduce novel targeted therapies for this disease. For example, imatinib has shown significant efficacy in the treatment of gastrointestinal stromal tumors with a functional mutation in the *c-KIT* gene.[14] In addition, angiogenesis inhibitors have produced significant advances in the clinical treatment of several tumors including lung, colorectal, ovarian, and renal carcinomas. A majority of soft tissue sarcomas have been discovered to have the increased expression levels of proangiogenic growth factors that contribute tumor angiogenesis, growth, and progression. Microvessel density was especially higher in liposarcoma and malignant fibrous histiocytoma.[15] In a phase II study, sunitinib showed potent activity in metastatic liposarcomas, with a median PFS of 3.9 months. The 3-month PFS rates in the untreated and pretreated liposarcoma patients were 75.0% and 69.2%, respectively.[16] Other targeted drugs such as sorafenib, pazopanib in combination with or without radiotherapy appeared to demonstrate acceptable antitumor activity in liposarcomas.[17,18]

Apatinib, a compound derived from valatinib, is an oral, highly potent inhibitor of VEGFR-2 tyrosine kinase targeting the intercellular ATP-binding site of the receptor, downregulating the phosphorylation, and subsequent downstream signaling. The antitumor activity and inhibition of angiogenesis of apatinib was investigated in different established human tumor xenograft model.[19] In vitro studies showed that apatinib exerted a significant inhibition of the kinase activities of VEGFR-2, c-kit, and c-src, and suppression of cellular phosphorylation of VEGFR-1, c-kit, and PDGFRβ.[19] In the phase III study of apatinib, patients were randomized to receive oral apatinib (850 mg once daily) or placebo at a ratio of 2:1. Apatinib significantly improved median overall survival (OS) time (6.5 months vs 4.7 months; $P=0.015$) and PFS time (2.6 months vs 1.8 months; $P<0.001$) in metastatic gastric cancer patients who progressed on two or more lines of chemotherapy.[7] Hand-foot syndrome, proteinuria, and hypertension were the most common treatment-related nonhematologic adverse events of apatinib, similar to other antiangiogenic agents. However, serious side effects, such as gastrointestinal massive hemorrhage and perforation, were not observed in the treatment arm. Only Li et al[20] recently presented a case of gastrointestinal massive hemorrhage and perforation during treatment of advanced gastric cancer with oral apatinib as the third-line chemotherapy. In addition, apatinib also showed potent activity against lung, breast and, colon cancer.[8,9] Ji et al[21] recently reported the first case of advanced malignant fibrous histiocytoma of the right forearm that had a partial response to apatinib.

The patient in this case report presented with extensive intra-abdominal and pelvic lesions and metastatic disease to the liver, with round cell liposarcoma variant, and refused to receive chemotherapy for palliation only. She was also recommended to receive sunitinib based on the data from a phase II study showing the efficacy of sunitinib in patients with advanced liposarcoma.[16] However, she did not afford the cost of sunitinib and finally choose apatinib. Administration with apatinib monotherapy produced a promising response, with manageable side effects. At immunohistochemistry, the section showed positive staining for CD31 and CD34. A large number of immature and intermediate blood vessels were found in the tumor area, and a strong positive staining for VEGF-2 was also observed in most cancer cells. Thus, these findings seem to be in line with the efficacy of the application of the antiangiogenic therapy for this patient.

4. Conclusions

As a novel tyrosine kinase inhibitor of VEGFR-2, apatinib has been only approved by China State Food and Drug Administration for the treatment of metastatic gastric cancer refractory to chemotherapy as a third-line treatment option. In this case report, it exerted good efficacy and safety in the treatment of a variety of solid tumors. A subgroup of advanced liposarcomas may be responsive to apatinib. It is possible that apatinib might be a feasible option in liposarcoma as the first treatment in metastatic setting. Large retrospective and prospective trials are needed to further confirm the efficacy and safety of apatinib in the clinical treatment of liposarcomas and other type of sarcomas.

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