Clinical Case Report

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Treatment of uterine high-grade endometrial stromal sarcoma with apatinib combined with chemotherapy

A case report

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Abstract

Rationale: The standard treatment for uterine high-grade endometrial stromal sarcoma (HGESS) is chemotherapy after surgery. However, the traditional combination chemotherapy has certain limitation, for example, the cancer cells will quickly become resistant to the chemotherapy drugs. Apatinib is a small-molecule antiangiogenic agent which has shown promising therapeutic effect against diverse tumor, but it still remains unknown whether apatinib has an antitumor effect in patients with endometrial stromal sarcoma (ESS). Here, we report a case of pulmonary metastasis from uterine HGESS successfully treated with apatinib combined with chemotherapy. We also review relevant literature discussing treatment of ESS.

Patients concerns: A 54-years-old Chinese woman complained of intermittent pain in the waist and abdomen for 4 months. The patient was diagnosed as uterine fibroids before operation. The surgeon performed a total hysterectomy with bilateral salpingo-oophorectomy, resection of peritoneal disseminated lesions, and the pathological examination revealed a HGESS.

Diagnosis: Uterine HGESS stage IV with lung metastases.

Interventions: The patient underwent surgery, chemotherapy, chemotherapy combined with apatinib, apatinib maintenance therapy, and radioactive particle implantation for lung metastasis.

Outcomes: The patient experienced the above interventions and achieved good results. And continue oral apatinib (500 mg daily) as maintenance therapy. It has been 16 months since the initial diagnosis, and the patient is still in follow-up.

Lessons: Apatinib combined with chemotherapy and apatinib monotherapy as maintenance therapy could be a new therapeutic strategy for ESS.

Abbreviations: CT = computed tomography, ESS = endometrial stromal sarcoma, HGESS = high-grade endometrial stromal sarcoma, LGESS = low-grade endometrial stromal sarcoma, PR = partial response, UUS = undifferentiated uterine sarcoma, VEGFR = vascular endothelial growth factor receptor, WHO = World Health Organization.

Keywords: apatinib, endometrial stromal sarcoma, high grade, targeted therapy

1. Introduction

Endometrial stromal sarcoma (ESS) is a tumor derived from endometrial stromal cells and is a rare uterine malignancy with a prevalence of less than 2% of all uterine tumors,[1] However, it is the second common uterine interstitial tumor.[1–2] In the end of 2014, World Health Organization classified ESS into low-grade endometrial stromal sarcoma (LGESS) high-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) based on the clinical and pathological features of ESS combined with molecular genetic studies.[3] vascular endothelial growth factor receptor (VEGF), as one of the most potent angiogenic factors, is a signal protein secreted by many solid cancers. Apatinib is a novel tyrosine kinase inhibitor that selectively inhibits the VEGF-2. It has exhibited potent antitumor effects multiple solid cancers. Here we report a case of uterine HGESS treated with apatinib and chemotherapy.

2. Case report

A 54-years-old Chinese female patient complained of intermittent pain in the waist and abdomen for 4 months. The gynecological examination revealed that the uterus was irregularly enlarged, measuring 9 cm × 9 cm × 8 cm. The texture of the uterus was hard, the activity was poor, and the tenderness was positive. Gynecological ultrasound showed multiple uterine fibroids (the largest one was 54 mm × 42 mm). Based on the above information, the patient was diagnosed as uterine fibroids before operation. Later she underwent a total hysterectomy and bilateral

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The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University. Written informed consent was obtained from the patient for publication of this case report.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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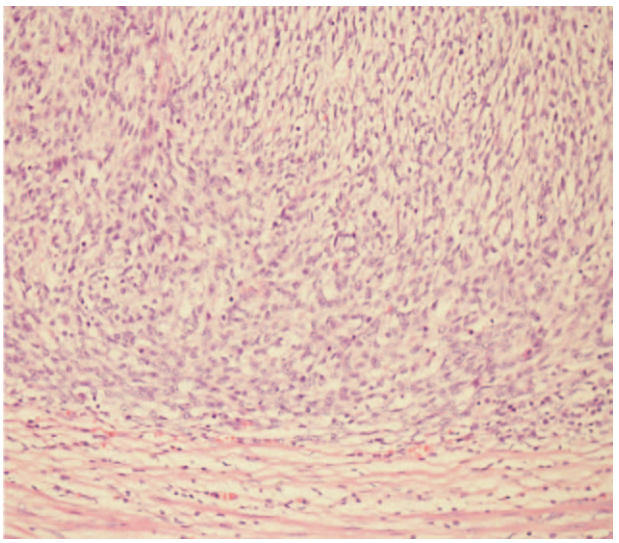

Figure 1. High-grade endometrial stromal sarcoma (hematoxylin-eosin, original magnification 20).

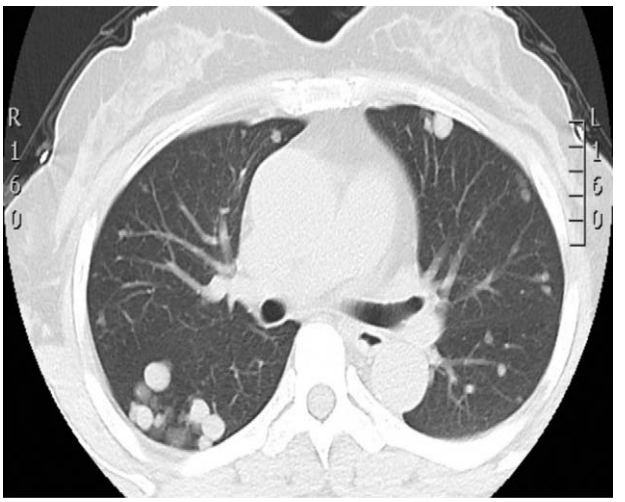

Figure 3. The diameter of lung lesions gradually increased about 90% (0.2–1.9 cm).

salpingo-oophorectomy, but the intraoperative findings and pathological examination hinted sarcoma. Consequently, the surgeon performed a total hysterectomy with bilateral salpingo-oophorectomy, resection of peritoneal disseminated lesions, and postoperative pathology examination revealed a HGESS (Fig. 1). Immunohistochemical examination showed: Ki-67 (+40%), SMA(−), ER(−), Desmin(−), H-caldesmon(−), PR(−), CD10 (−), WT-1(+), Cyclin D1(+). Subsequently, a computed tomography (CT) scan (Fig. 2) revealed multiple lung nodular lesions (diameter, 0.3–1.0 cm). Therefore, the patient was clinically diagnosed as HGESS stage IV with lung metastases. The chemotherapy (gemcitabine 1000 mg/m^2 day 1 day 8, docetaxel 75 mg/m^2 day 1) was performed for 2 cycles, and the diameter of lung lesions gradually increased about 90% (0.2–1.9 cm) (Fig. 3), which showed progressive disease. Considering that angiogenesis is one of the basic factors for tumor cell growth. We started a chemotherapy regimen (doxorubicin 20 mg/m^2 day 1–day 3, ifosfamide 2000 mg day 1–day 3) combined with oral apatinib (250 mg daily, minimum dose) without major toxicity. After about 4 months of treatment—6 cycles of chemotherapy, the patient underwent a restaging computed tomography (CT) scan. The result displayed that the lesions, which had a diameter about 0.3 to 0.6 cm, were reduced in size (Fig. 4). We evaluated the disease as partial response (PR). After that, apatinib was given as maintenance therapy. Subsequently, regular CT scan showed that the lung lesions was stable and their size were maintained at 0.3 to 0.6 cm, which was a tumor-bearing state. After 8 months, the lung lesions increased to 0.3 to 2.0 cm (Fig. 5), Considering the progression of the disease, we gave the patient radioactive particle implantation for lung metastasis and apatinib (500 mg daily) as maintenance therapy, no obvious discomfort after the operation. So far, there has been no apparent recurrence or metastasis of her disease. Occasionally, side effects such as hypertension (grade II), mild hand-foot reaction, urinary protein

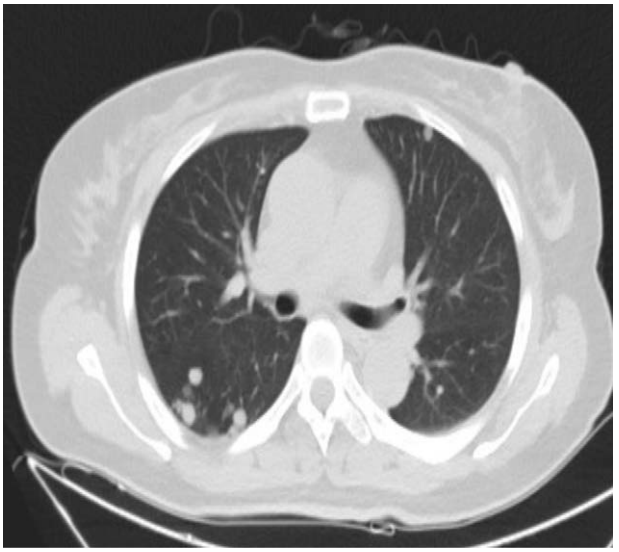

Figure 2. A computed tomography scan revealed multiple lung lesions (diameter, 0.3–1.0 cm).

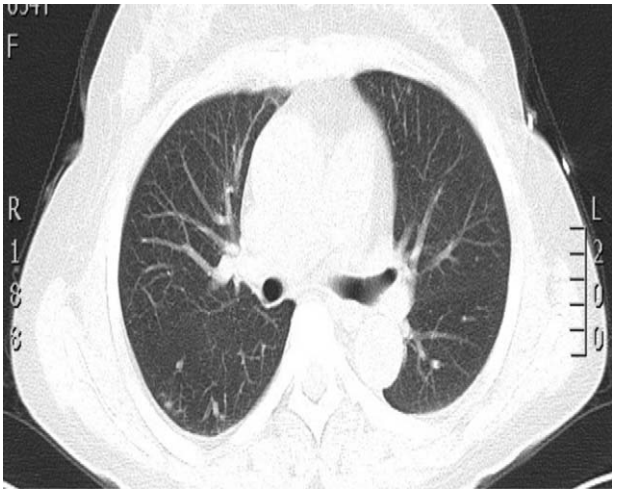

Figure 4. The lesions' masses were reduced: had a diameter about 0.3 to 0.6 cm.

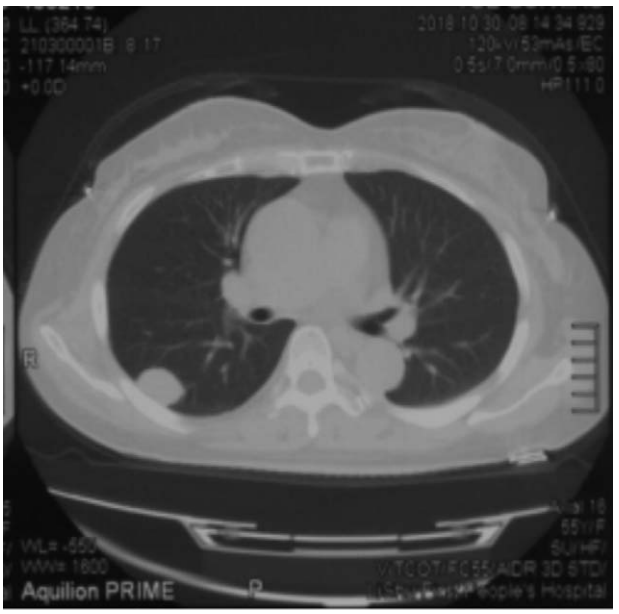

Figure 5. After several months, the lung lesions increased to 0.3 to 2.0 cm.

(3+), and hemorrhinia occurred, but the patient could tolerate the above effects.

3. Discussion

The incidence of HGESS is rare. The average age of patients is about 50 years old. The clinical manifestations are atypical. They often show abnormal genital bleeding, abdominal pain, and pelvic mass. Due to the low incidence of HGESS, there is lack of specific clinical manifestations and biomarkers, also the imaging features are atypical which lead to a high rate of misdiagnosis as uterine fibroids. HGESS has a poor prognosis. Most patients are advanced (stages III to IV) at the time of initial diagnosis, and at the same time lung metastases are most common. Seen from the naked eye, the cut surface of HGESS is mostly fish-like, often accompanied by areas of extensive bleeding and necrosis. Observed from the microscope, densely cellular tumor with sheets and nests comprising a variable admixture of high-grade round cell elements and lower-grade spindle cell elements. The round cells show irregular hyperchromatic or granular nuclei and scanty cytoplasm. And only have slight characteristics of endometrial stromal cell differentiation.[1,4–5] In our report, the patient was also misdiagnosed as uterine fibroids at the time of initial diagnosis. During the operation, according to the gross finding, we realized that there was a possibility of uterine malignancy tumor, and performed a comprehensive staging operation, at the same time lung metastasis was found after surgery. Corresponding the surgical pathology staging, which was based on the 2009 International Federation of Obstetrics and Gynecology,[2] the patient was diagnosed as HGESS stage IV, lung metastases, which was consistent with the clinical and pathological features of HGESS.

HGESS has a high risk of recurrence and metastasis, therefore postoperative adjuvant therapy play an important role. Up to now, pelvic external radiotherapy has been widely used as an adjuvant therapy for HGESS, which can reduce postoperative pelvic recurrence, but cannot improve the overall survival rate of patients, which may be related to extrapelvic metastasis.[6] Because its high risk of distant metastasis, adjuvant chemotherapy is still an important part of comprehensive treatment, and a study by Pautier et al[7] also showed the benefits of adjuvant chemotherapy. Commonly used chemotherapy regimens for HGESS includes gemcitabine combined with docetaxel, doxorubicin combined with ifosfamide, doxorubicin combined with dacarbazine, gemcitabine combined with dacarbazine, and so on,[8] of which the gemcitabine combined with docetaxel is the most widely used. In this case, the patient was initially treated with "Gemcitabine combined with Docetaxel" regimen, and after 2 courses of treatment, we evaluated the disease as progression, subsequently, we gave her "liposome doxorubicin plus ifosfamide" regimen combined with oral apatinib, the effect was significant, evaluated as PR. A Chinese study[9] showed that for patients with HGESS, the use of "doxorubicin plus ifosfamide" VS "gemcitabine plus docetaxel" regimen, the efficiency is consistent, are 60%. Therefore, the patient achieved the efficacy of PR, we presume that apatinib played a certain role in this treatment regimen. But this has yet to be confirmed by further clinical research.

Targeted therapy for ESS has been widely concerned; however, due to the lack of large-scale clinical studies, only case reports are available. Pazopanib is a multitarget tyrosine kinase inhibitor, and the National Comprehensive Cancer Network uterine oncology clinical practice guidelines (Version 1.2016) have included pazopanib as one of the drugs available for systemic treatment of uterine sarcoma.[8] Apatinib is a VEGFR-2 intracellular inhibitor on the vascular endothelial cell membrane, which blocks the downstream signaling and inhibits neovascularization in tumor tissue by highly selective competition for the ATP binding site of VEGFR-2 in cells. Therefore, it exerts a powerful antitumor effect and has been proved to be a new treatment option. It has therapeutic effects for various types of tumors, with remarkable curative effect and controllable safety.[10] As early as 2014, the Chinese Food and Drug Administration has approved apatinib as a follow-up treatment for patients with advanced gastric cancer. To date, a series of Phase II or Phase III clinical trials of apatinib in various cancers such as non-small cell lung cancer, breast cancer, hepatocellular carcinoma, and sarcoma have been completed or are underway.[11–14]

HGESS has a high degree of malignancy and is prone to recurrence and metastasis. However, its prognosis is between LGESS and UUS. Compared with LGESS, recurrence of HGESS patients is more common, and the recurrence time is earlier (often <1 year), and more likely to lead to death, not to mention advanced HGESS patients. In this report, patients treated with apatinib combined with traditional chemotherapy have achieved good results. Later, the patient received radioactive particle implantation for lung metastasis. Continue oral apatinib (500 mg daily) as maintenance therapy after surgery. It has been 16 months since the initial diagnosis, and the patient is still in follow-up. We expect patients to have longer overall survival. Therefore, vascular targeted drugs combined with traditional chemotherapy are expected to become a new choice for the treatment of ESS. It is hoped that clinicians can carry out relevant clinical trials and explore new treatment options to prolong the survival of patients and improve their quality of life.

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