Case Report

Colorectal leiomyosarcoma with *BRCA2* mutation benefit from treatment with olaparib: a case report

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Background: Colorectal leiomyosarcoma (LMS) is a rare colorectal malignancy accounting for approximately 1% of all colorectal malignancies with a poor prognosis and limited treatment options. Targeted therapies have been applied for breast cancer 2 (*BRCA2*) alterations, but their role remains to be explored in colorectal LMS. This case could provide clinical proof for the application of olaparib for LMS patients.

Case Description: Here, we present a case of colorectal LMS with *BRCA2* alterations who was treated with olaparib and achieved progression-free survival (PFS) for 1 year. In August 2016, a 46-year-old female patient was admitted to hospital due to a mass in the left lower abdomen and was diagnosed with LMS of the sigmoid colon. After surgical resection, chemotherapy with ifosfamide or ifosfamide combined with pirarubicin was given and achieved stable disease (SD) until the disease progressed 1.5 years later. Afterwards, a multi-target tyrosine kinase inhibitor, anlotinib, was taken. Before the observation of lung and liver metastasis, the patient's disease was stable for 1 year. *BRCA2* mutation and rearrangement was revealed by next-generation sequencing (NGS), and the targeted therapy, olaparib, was given. Efficacy evaluation showed SD for 1 year, and no obvious toxic and side effects were observed.

Conclusions: Our case suggested that NGS should be considered for further treatment of patients with colorectal LMS, and poly (ADP-ribose) polymerase (PARP) inhibitors could be a feasible therapy for LMS patients with *BRCA2* alterations.

Keywords: Colorectal leiomyosarcoma (colorectal LMS); breast cancer 2 alterations (*BRCA2* alterations); olaparib; next-generation sequencing (NGS); case report

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Introduction

Colorectal leiomyosarcoma (LMS) is extremely rare and accounts for approximately 1% of all colorectal malignancies (1). It has a high propensity to recur and to metastasize at distant sites (liver and lungs) by hematogenous spread (2,3). According to the guideline of the National Comprehensive Cancer Network (NCCN), the standard radical treatment modality for colorectal LMS is surgical resection, and systemic therapy is recommended. Nevertheless, its prognosis remains poor, with a 5-year overall survival rate of 43.8% (4). To date, only HER3-E332E synonymous mutation and somatic MED12 mutations were reported in retroperitoneal LMS and uterine LMS (uLMS), respectively (5,6). However, little is known about its molecular heterogeneity and no targeted therapy currently exists for LMS. In this case report, we presented a patient diagnosed with LMS of the sigmoid colon. This patient tested positive for breast cancer (*BRCA*) mutation and rearrangement by next-generation sequencing

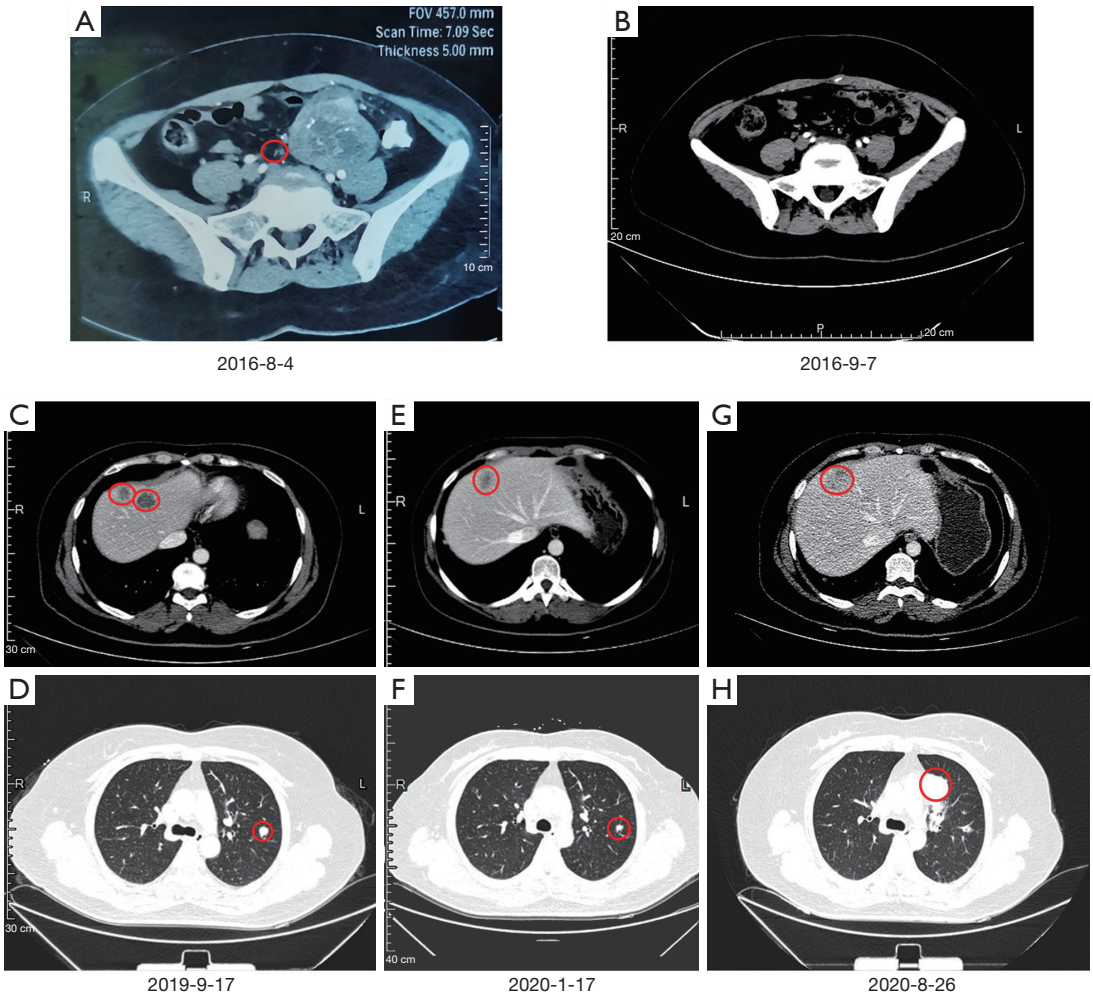

Figure 1 The CT images of the tumor lesions during treatment. (A) Baseline: a mass in the left pelvic cavity. (B) After surgery, no lesion could be observed. (C,D) Liver and lung metastases after anlotinib treatment. (E,F) Three months after olaparib therapy, reduced lesions were observed in the liver and lungs. (G,H) Increased metastatic lesions in both the lungs and liver in August 2020. Red circles represent the location and size of the lesions. R indicated the right side, and L indicated the left side in the CT images. CT, computed tomography.

(NGS), and had benefited from the targeted therapy, olaparib, for nearly a year. Our study verified for the first time that the application of NGS may help determine further treatment options for LMS, and PARP inhibitors may be a feasible therapy for LMS patients with *BRCA2* alterations. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-419/rc).

Case presentation

In August 2016, a 46-year-old female patient was admitted to another hospital due to a mass in the left lower abdomen. The computed tomography (CT) images during the diagnosis and treatment were shown in *Figure 1*, and the hematoxylin-eosin (HE) staining images were shown in *Figure 2*. Enhanced abdomen CT showed a mass in the left pelvic cavity (*Figure 1A*), with a high possibility of stromal tumor. A small amount of effusion was observed in the lacunae of the uterus and rectum. No obvious contraindication was found. Under general anesthesia, transabdominal tumor resection was performed (*Figure 1B*), and the postoperative pathology showed multiform LMS in the mesenterium of the sigmoid colon which invaded the surrounding intestine tissues and adhered to the left adnexa uteri. Tumor embolus could be seen in both the tumor

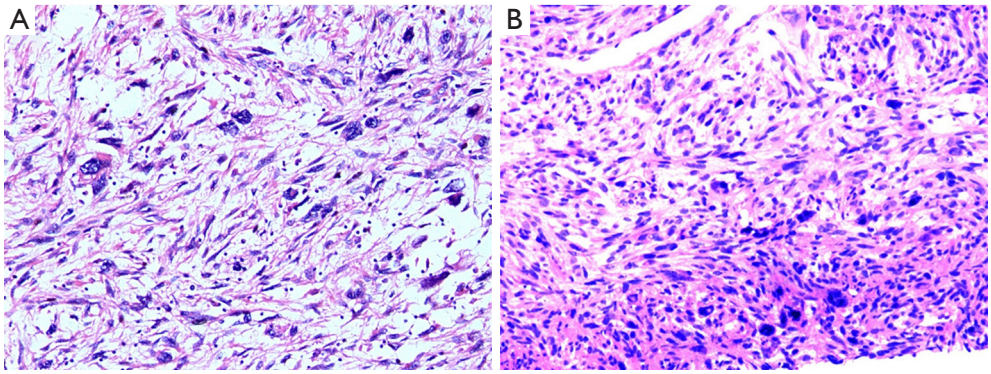

Figure 2 HE staining of the tumor tissues. (A) HE staining of the surgical tissues from the sigmoid colon showed spindle cell mesenchymal malignancy in 2016 (40×). (B) HE staining of the biopsy from the liver metastatic lesion showed spindle cell type tumor tissue in 2020 (40×). HE, hematoxylin-eosin.

and the left ovarian vessel. Mesenteric lymph nodes (0/2) showed no tumor metastasis. The immunohistochemistry (IHC) findings were as follows: CD117 (–), CD34 (+), CD68 (–), Cal (–), CKPAN (–), Desmin (+), SMA (+), SMMS-1 (+), Vimentin (+), S-100 (–), and Ki67 (+75%). In September 2016, the patient was referred to our hospital (The Fourth Hospital of Hebei Medical University) for further diagnosis and treatment. After admission, enhanced CT showed micronodules in the left upper lobe and no tumor recurrence or metastasis was observed. One cycle of monotherapy with ifosfamide was given. Pathological consultation was conducted in October 2016. The IHC results were as follows: CR (–), CK (–), SMA (–/+), Des (+), CD68 (–), Ki-67 (>50%), CD34 (+), and CD17 (–). According to these IHC results and the observed spindle cell mesenchymal malignancy, the diagnosis was revised as pleomorphic liposarcoma of the sigmoid colon at stage IIIB (*Figure 2A*). Further IHC or genetic testing was recommended but refused by the patient. Ifosfamide chemotherapy was continued for 4 cycles, and the efficacy evaluation showed no obvious signs of recurrence or metastasis. Subsequently, the patient was given 2 cycles of ifosfamide combined with pirarubicin.

In April 2018, enhanced CT showed multiple small nodules in the lung and calcification at the right edge of the liver. The pulmonary nodules were too small to puncture, so the patient was discharged for observation. In September 2018, positron emission tomography (PET)-CT reexamination revealed multiple high-density nodules in the lung, some of which showed abnormal glucose hypermetabolism. In addition, small nodular calcification was observed in the right lobe of the liver (S6), indicating progressive disease (PD). The patient received anlotinib (12 mg/day) and achieved progression-free survival (PFS) for 1 year (*Figure 1C,1D*).

On September 29, 2019, the surgical tissue was sent for NGS analysis, and the result revealed *BRCA2* mutation and *FRYI-BRCA2* rearrangement, with tumor mutational burden (TMB) =5 Muts/MB and microsatellite stable (MSS). Based on the NGS analysis result, the patient started on targeted therapy with olaparib. In January 2020, 3 months after olaparib therapy, CT reexamination showed reduced lesions in the liver, and the efficacy evaluation was stable disease (SD) (*Figure 1E,1F*). However, in August 2020, enhanced CT showed increased metastatic lesions in both the lung and liver (*Figure 1G,1H*), indicating PD. In September 2020, liver biopsy was performed, and the pathological report showed spindle cell type tumor tissue (*Figure 2B*). Additionally, a few atypical cells were seen on the histocytological smear of the biopsy. Combined with the IHC results [Des (+), Calponin (+), S100 (–), MDM2 (–)], pathological consultation revised the diagnosis as mesangial LMS of the sigmoid colon with multiple metastases (liver and lung) after postoperative chemotherapy.

Doxorubicin hydrochloride liposome infusion was administered in September 2020, but the patient had poor appetite and fatigue. In November 2020, the treatment was adjusted to doxorubicin hydrochloride liposome + apatinib, and the efficacy evaluation was PD after 3 cycles. In December 2020, olaparib + apatinib was used for treatment, and the effect was evaluated as PD after 3 months. In March 2021, the patient was given camrelizumab + apatinib

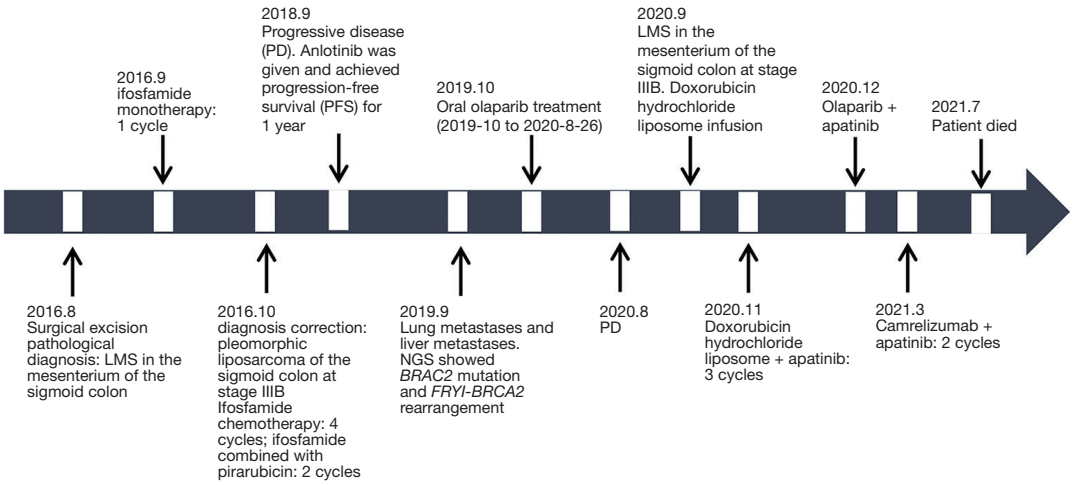

Figure 3 Timeline showed briefly the diagnosis, treatment, progression, and prognosis of this case. LMS, leiomyosarcoma; PD, progressive disease; PFS, progression-free survival; NGS, next-generation sequencing; BRCA2, breast cancer 2.

for 2 cycles, after which the patient developed intestinal obstruction. The follow-up was mainly palliative treatment. The patient died in July 2021. The treatment timeline was shown in *Figure 3*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

Discussion

Colorectal LMS is a rare malignancy with an unfavorable prognosis. According to the National Cancer Data Base in the USA, only 433 patients were diagnosed with primary colorectal sarcoma, of which 57.5% had colorectal LMS (2). To achieve complete removal of the tumor with negative margins, surgical excision is widely accepted for colorectal LMS. Ifosfamide or ifosfamide + epirubicin are recommended by both the NCCN guideline and the Chinese Society of Clinical Oncology (CSCO) guideline. Nevertheless, despite the recommendations, the effectiveness of systemic therapy remains controversial since the majority of LMS cases are relatively insensitive to chemotherapeutic agents (7). Consistently, in this case, ifosfamide and ifosfamide + epirubicin were applied postoperatively for 5 months, however, the disease progressed 1.5 years later.

Considering that anlotinib showed great efficacy and safety for soft tissue sarcomas (STS) including LMS in a multicenter, single-arm, phase II study (8), and the fact that no standard second-line treatment was available at that time in China for patients with STS who progressed after first-line chemotherapy, the patient began to take anlotinib after PD in September 2018. The patient achieved PFS for 1 year until liver and lung metastases. Subsequently, a phase IIB trial (ALTER0203) revealed the efficacy and safety of anlotinib for STS in 2018 American Society of Clinical Oncology (ASCO), and the results showed that anlotinib significantly prolonged the PFS (6.27 *vs.* 1.47 months) of STS, reduced the risk of disease progression by 67%, and significantly improved the disease control rate (DCR). In May 2019, anlotinib was recommended as a second-line therapy for advanced STS by the CSCO, verifying that our treatment strategy was prospective and correct.

After the observation of liver and lung metastases, no further treatment option was available; hence, the patient sought precision medicine of targeted therapy by NGS analysis, and *BRCA2* mutation and rearrangement were uncovered. *BRCA* (*BRCA1* and *BRCA2*) are tumor-suppressor genes that are associated with the homologous recombination (HR) pathway and help to repair damaged DNA. In hereditary breast and/or ovarian cancer, the *BRCA1* and *BRCA2* genes are the most clinically important genetic predictors and account for 5% to 15% of these 2 cancers (9). *BRCA1/2* alterations usually lead to functional defects in double-stranded DNA-break repair in breast and ovarian cancers, which sensitizes them to poly (ADP-ribose)

polymerase (PARP) inhibitors such as olaparib (10,11) and veliparib (12). In STS, Movva *et al.* reported that *BRCA2* gene alterations occurred at a rate of 17.6% in 2539 sarcoma specimens (13), while Seligson *et al.* showed that 10% of uLMS tumors had a *BRCA2* alteration, and also presented 4 uLMS patients with *BRCA2* loss who benefited from PARP inhibitors (14). Nevertheless, no studies or case reports have been published on colorectal LMS with *BRCA2* alteration and the corresponding treatment so far. Here, after multiple treatment failures, the patient was found to have *BRCA2* mutation and rearrangement by NGS, and gained clinical benefit for 1 year after targeted therapy with the PARP inhibitor olaparib. This suggests that NGS is a powerful tool for guiding clinical administration, especially for rare tumors with limited therapeutic regimens. Olaparib also extended survival in colorectal LMS patients with *BRCA2* mutations. If the case was given olaparib as early as possible, the prognosis may differ.

In conclusion, we present a patient with mesangial LMS of the sigmoid colon. After progression on chemotherapy and anlotinib treatment, the patient was found to have *BRCA2* mutation and rearrangement by NGS, and obtained clinical benefit for 1 year with targeted therapy by olaparib. As evidenced by our case, the application of NGS may help determine further treatment options for LMS, and PARP inhibitors may be a feasible therapy for LMS patients with *BRCA2* alterations.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-419/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-419/coif). SZ and MX are employees of Shanghai OrigiMed Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

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