Case Report

Using a combination of fruquintinib, raltitrexed, and S-1 as a third-line treatment for metastatic colorectal cancer with co-existence of Hodgkin lymphoma: a case report

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Background: Patients with metastatic colorectal cancer (mCRC) beyond second line treatment have a poor prognosis. Fruquintinib, regorafenib, trifluridine/tipiracil (TAS-102), panitumumab and cetuximab combined with single-agent chemotherapy regimens are currently recommended as third-line therapies for patients exhibiting disease progression. Effective late-line therapies for mCRC are urgently needed. The FRESCO randomized clinical trial (RCT) prompts fruquintinib as a third-line treatment in advanced colorectal cancer (CRC). A phase II study in our center reported the efficacy and safety of S-1 plus raltitrexed for the treatment of chemo-refractory mCRC. The combination of the fruquintinib, raltitrexed, and S-1 has not been reported in mCRC.

Case Description: This case report presents a patient with mCRC who received third-line treatment with fruquintinib, raltitrexed, and S-1. A 54-year-old male presenting with hematochezia was admitted to West China Hospital of Sichuan University in June 2017 and underwent surgery for a tumor between the rectum and sigmoid colon. Postoperative pathology identified adenocarcinoma (wild-type RAS/RAF, no PIK3CA mutation), and the patient was diagnosed with mCRC (pathological stage, pT3pN1apM0). The mFOLFOX6 regimen was administered. The patient was subsequently diagnosed with Hodgkin lymphoma in May 2018 and treated with the ABVD regimen after multidisciplinary discussions. Liver metastases (intestinal-type adenocarcinoma) were detected in November 2018, and second-line therapy with the FOLFIRI regimen was initiated in January 2019. Lung metastases were identified in September 2019, so the patient was treated with a combination of raltitrexed, S-1, and fruquintinib. A partial response (PR) was detected in November 2019, and the patient underwent resection of the hepatic lesion on November 5, 2020. Computed tomography (CT) images in November 2021 revealed a stable disease; thus, raltitrexed was discontinued, and S-1 and fruquintinib were maintained. The treatment is still responding until the last follow-up (December 2022).

Conclusions: The case was characterized by the simultaneous existence of mCRC and Hodgkin lymphoma, which required management by a multidisciplinary team. Third-line therapy with fruquintinib, raltitrexed, and S-1 achieved a PR that permitted surgical resection and enabled a relatively long progression-free survival. The findings suggest that the three agents regimen might be clinically effective as late-line therapy for mCRC.

Keywords: Colorectal cancer (CRC); metastasis; chemotherapy; vascular endothelial growth factor receptor inhibitor (VEGFR inhibitor); case report

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Introduction

Patients with metastatic colorectal cancer (mCRC) have a poor prognosis and the 5-year overall survival for stage IV disease is a dismal 11% (1). The classical first- and second-line therapies for mCRC are based on the FOLFOX [folinic acid, 5-fluorouracil (5-FU), and oxaliplatin] and FOLFIRI (folinic acid, 5-FU, and irinotecan) regimens (2,3). However, many patients on these standard therapies experience disease progression. Fruquintinib, regorafenib, trifluridine/tipiracil (TAS-102) are now available as third-line therapies for mCRC following the failure of first- and second-line chemotherapy regimens (2-4). Randomized controlled trial (RCT) comparing the efficacy and safety of fruquintinib, regorafenib and TAS-102 as third-line therapy in mCRC are lacking. Indirect comparison suggested that the three agents had similar OS but that fruquintinib was superior in terms of PFS and DCR compared with that of TAS-102 (4-6). However, Patients with mCRC beyond second line treatment have a poor prognosis. More third-line treatment regimens are badly needed.

Most patients with mCRC receive long-term treatment with 5-FU and/or 5-FU analogs. An important mechanism underlying resistance to 5-FU, especially secondary resistance, involves the up-regulation of dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS), and inhibition of these enzymes can reverse resistance to 5-FU (7,8). S-1 consists of tegafur, 5-chloro-2-4-dihydroxypyridine (which inhibits DPD), and oteracil potassium, while raltitrexed is a TS-specific inhibitor. A phase II study reported that S-1 plus raltitrexed was safe and effective for the treatment of chemo-refractory mCRC (9). Another phase II study demonstrated that third-line therapy with S-1, raltitrexed, and bevacizumab achieved good efficacy in patients with mCRC (10). A small sample retrospective study also suggested low-dose apatinib plus S-1 was a potential alternative regimen for the treatment of refractory mCRC with tolerable and controlled toxicity (11). These findings strongly suggest that late-line treatment with a combination of chemotherapeutic and antiangiogenic agents have beneficial effects in patients with mCRC.

Fruquintinib is a vascular endothelial growth factor receptor (VEGFR) inhibitor that highly selectively binds to and inhibits VEGFR-1, -2, and -3. The FRESCO study demonstrated the beneficial effects of fruquintinib monotherapy as a third-line treatment for mCRC (12). Fruquintinib monotherapy has already been approved by the Center for Drug Evaluation of China as third-line chemotherapeutic drug for mCRC.

This case report presents a patient with mCRC who developed Hodgkin lymphoma as a second malignancy, requiring careful cooperation between members of a multidisciplinary team to optimize the treatment of both cancers. Notably, following the failure of the mFOLFOX6 and FOLFIRI regimens, the patient responded well to third-line chemotherapy using fruquintinib, raltitrexed, and S-1. This case raises the possibility that regimens based on a combination of fruquintinib, raltitrexed, and S-1 could be used as late-line therapies for mCRC. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-39/rc).

Highlight box

Key findings

- The case was characterized by the simultaneous existence of mCRC and Hodgkin lymphoma. The findings suggest that the combination of fruquintinib, raltitrexed, and S-1 might be clinically effective as late-line therapy for mCRC.

What is known and what is new?

- Patients with mCRC beyond second line treatment have a poor prognosis. The FRESCO trial prompts fuquinitinib as a third-line treatment in advanced colorectal cancer. A phase II study in our center reported the efficacy and safety of S-1 plus raltitrexed for the treatment of chemo-refractory mCRC.
- The combination of the three agents has not been reported, and the case demonstrated the efficacy and safety of the third-line therapy with fruquintinib, raltitrexed, and S-1 in mCRC.

What is the implication, and what should change now?

- This case provides new insight into third-line treatment options for mCRC. Future studies with large sample size are needed to validate these discoveries.

Case presentation

A 54-year-old male patient was admitted to West China Hospital of Sichuan University due to hematochezia in June 2017. The timeline is shown in *Figure 1*. A colonoscopy showed a neoplasm between the rectum and sigmoid colon. Surgical resection, colorectal anastomosis, and enterolysis were performed in June 2017. Pathological evaluation of tumor specimens revealed the presence of adenocarcinoma with the wild-type RAS/RAF and without the *PIK3CA* mutation. The pathological stage was determined to be

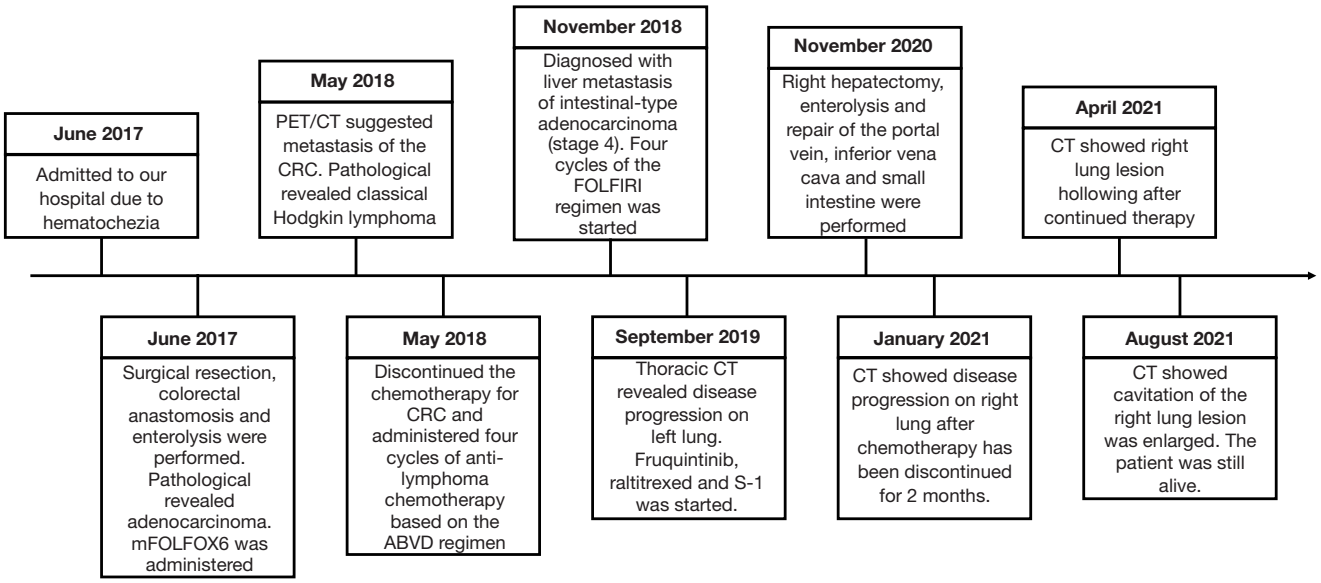

Figure 1 The timeline of the patient during the disease course. PET, positron emission tomography; CT, computed tomography; CRC, colorectal cancer.

pT3pN1apM0. Immunohistochemistry revealed positive expression of MLH1, MSH2, MSH6, PMS2 and CK20 but not CDX, and the Ki67 expression was 45%. Therefore, the mFOLFOX6 regimen (oxaliplatin 85 mg/m^2 i.v., leucovorin 400 mg/m^2 i.v., and 5-FU 400 mg/m^2 i.v. bolus on day 1 followed by 5-FU 2,400 mg/m^2 i.v. continuous infusion over 46–48 hours) was administered as adjuvant therapy after surgery without SAEs.

In May 2018, the patient reported dizziness, weakness, exhaustion, and fever without an evident cause. Positron emission tomography (PET) and computed tomography (CT) scanning revealed invasion of the right cervical and right supraclavicular lymph nodes by lymphoma (*Figure 2*). PET/CT scans also revealed lesions with increased glucose metabolism in the right lobe of the liver, which suggested hepatic metastasis of the colorectal cancer (CRC) (*Figure 3*). A biopsy showed hyperplasia of lymphoid tissues. Immunohistochemistry demonstrated large cells with positive expression of PAX-5, MUM-1, CD30, CD15, EBV, CXCL-13, and CD4 as well as a Ki-67 expression level of 50%. In situ hybridization detected EBER1/2. T cell receptor (TCR) gene rearrangement testing showed no clonal amplification of the TCRγ gene. The patient was diagnosed with classical Hodgkin lymphoma of mixed cellularity.

Following careful review and discussion of the case by the multidisciplinary team, the decision was made to discontinue the chemotherapy for CRC and administer 4 cycles of anti-lymphoma chemotherapy based on the ABVD regimen (doxorubicin 25 mg/m^2 i.v. over 5–10 minutes, bleomycin 10,000 IU/m^2 i.v. over 5–10 minutes, vinblastine 6 mg/m^2 i.v. over 5–10 minutes, and dacarbazine 375 mg/m^2 i.v. over 60 minutes on days 1 and 15). The lymphoma lesion showed a complete response after treatment. Re-examination by PET and CT in November 2018 showed substantial enlargement of the low-density shadow in the right liver lobe. Percutaneous liver biopsy plus radiofrequency ablation were performed as the lesion was solitary and had a diameter of less than or equal to 3 cm, and the pathological examination suggested adenocarcinoma. Taking into account the patient's medical history, the patient was diagnosed with liver metastasis of intestinal-type adenocarcinoma (stage IV).

The patient developed liver metastasis during the first-line treatment with a PFS of 11 months. Second-line therapy with 4 cycles of the FOLFIRI regimen (irinotecan 180 mg/m^2 i.v., leucovorin 200 mg/m^2 i.v. and 5-FU 400 mg/m^2 i.v. bolus on day 1 followed by 5-FU 600 mg/m^2 i.v. continuous infusion over 22 hours) was started in January 2019. Subsequently, CT scans of the thorax and abdomen revealed new nodular lesions in the posterior segment of the apex of the superior lobe of the left lung, as well as

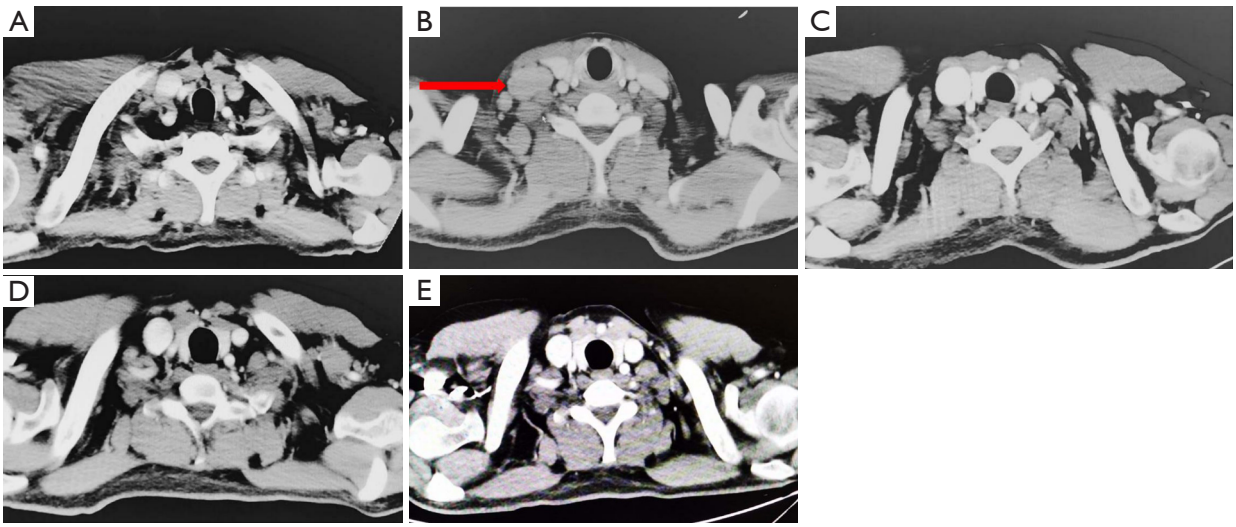

Figure 2 CT images showing the lymphoma. (A) CT on December 12, 2017, showed no lymphoma lesion. (B) CT on May 13, 2018. The red arrow shows the lymphoma lesion. (C) CT on May 16, 2019. (D) CT on April 26, 2021. (E) CT on November 15, 2021. CT, computed tomography.

enlargement of the lesion in the liver (September 2019; *Figure 3*). These findings indicated disease progression after 8 months of second-line treatments. Therefore, third-line therapy was initiated using 4-week cycles of raltitrexed 4 mg i.v. on day 1, S-1 75 mg PO on days 1–14, and fruquintinib 5 mg PO on days 1–21. Enhanced CT of the thorax and abdomen in November 2019 showed a partial response (PR) of the liver lesions to therapy (*Figure 3*). Upper abdominal CT in November 2020 demonstrated sporadic nodules and patchy shadows with slightly low density in the lower segment of the right liver lobe, and the margins of some lesions showed enhancement (*Figure 3*).

The patient now met the indications for surgery; therefore, a right hepatectomy, enterolysis, and repair of the portal vein, inferior vena cava, and small intestine were performed on November 5, 2020. Abdominal CT in January 2021 showed no evidence of tumor recurrence or further metastasis (*Figure 3*). Thoracic CT demonstrated a 0.7 cm diameter nodule at the posterior basal segment of the inferior lobe of the right lung (*Figure 4*). Therapy with raltitrexed, S-1, and fruquintinib was continued from January 2021. CT performed in April 2021 revealed cavitation of the lesion in the right lower lung, no change in the lesions in the left lung, and no recurrence of the liver lesion or lymphoma (*Figure 4*). In August 2021, CT showed that cavitation of the lesion in the right lower lung was enlarged (*Figure 4*). Furthermore, the carcinoembryonic antigen level fell from 140 to 1.86 ng/mL following therapy with these agents. The patient developed mild oral ulceration during treatment with raltitrexed, S-1, and fruquintinib, which improved after discontinuation of fruquintinib for 3 days. In November 2021, CT images showing the lymphoma, liver, and lungs revealed stable disease (*Figure 4*). Thus, raltitrexed was discontinued, and treatment of S-1 and fruquintinib was maintained. In April 2022, the patient was followed by a phone interview and reported grade 2 hypertension and a hand-foot skin reaction, which could be tolerated without a dose adjustment or interruption. The treatment is still responding until the last follow-up (December 2022) with a PFS of 38 months and the OS not yet reached.

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

This case report presents a patient with chemo-refractory mCRC who also developed Hodgkin lymphoma,

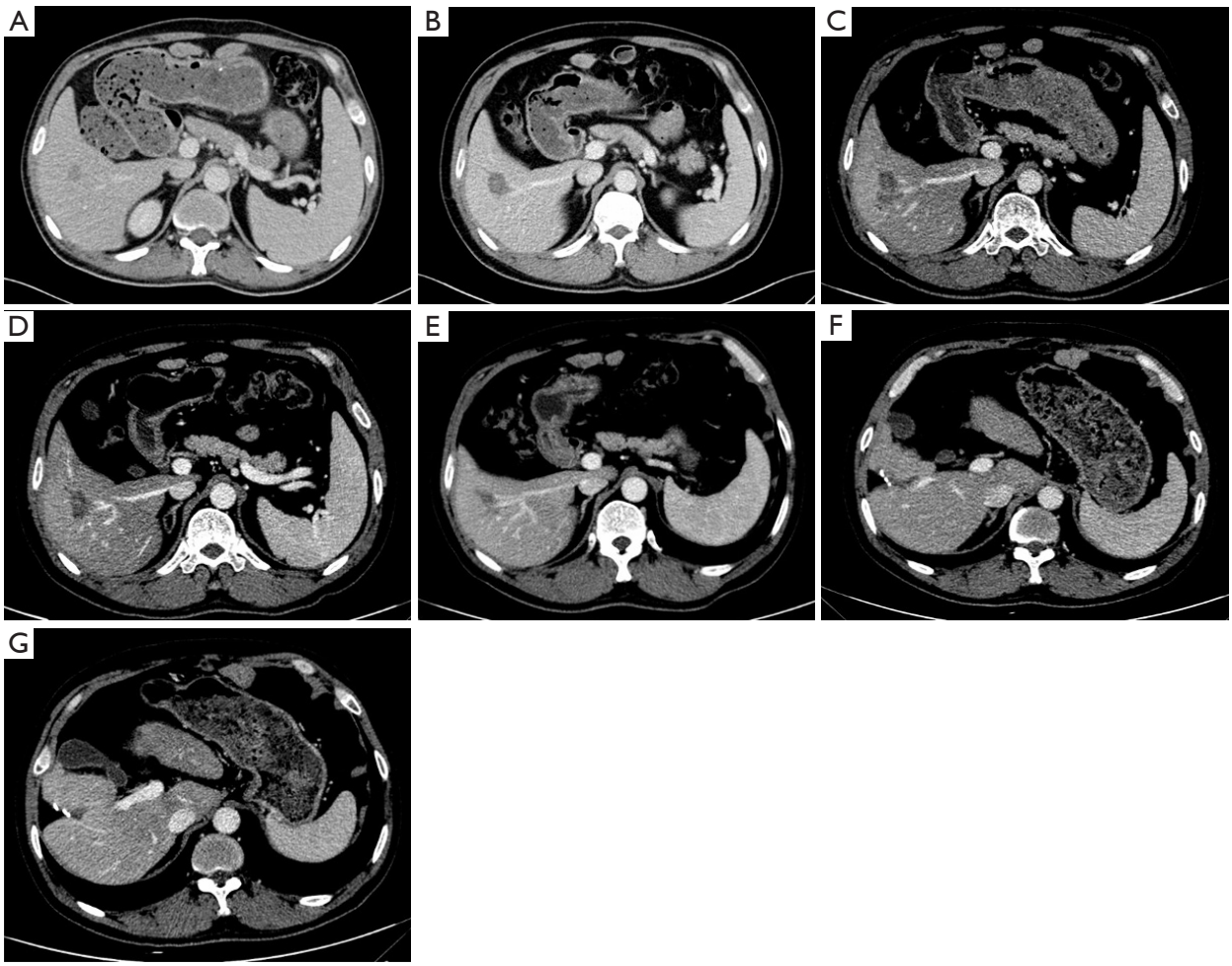

Figure 3 CT images of the liver. (A) CT on May 13, 2018, showed the presence of liver lesions, confirming metastasis of the CRC. (B) CT on May 16, 2019, indicated stable disease after second-line chemotherapy. (C) CT on September 24, 2019, demonstrated enlargement of the hepatic lesion, which indicated disease progression. (D) CT on November 25, 2019, showed a partial response of the liver lesions to therapy. (E) CT on November 4, 2020, showed that the indications for surgery had been met. (F) CT on January 18, 2021, provided no definite evidence of tumor recurrence after the operation. (G) CT on November 15, 2021, provided no definite evidence of tumor recurrence after the operation. CT, computed tomography; CRC, colorectal cancer.

necessitating careful management by a multidisciplinary team. Notably, the patient achieved a PR that allowed resection of the metastatic lesion in the liver as well as a relatively long progression-free survival (PFS) of 38 months after third-line therapy with fruquintinib, raltitrexed, and S-1. The overall survival (OS) has not yet reached. In addition, there were no SAEs during treatment with this drug combination.

A previous study demonstrated the efficacy and safety of S-1 plus raltitrexed in the treatment of chemo-refractory mCRC, with an objective response rate of 13.9%, a disease control rate of 58.1%, a median PFS of 107 days [95% confidence interval (CI): 96.3–117.7 days], and overall survival (OS) of 373 days (95% CI: 226.2–519.8 days) (9). Another investigation reported that third-line treatment with S-1, raltitrexed, and bevacizumab achieved a median PFS of 110 days (95% CI: 65.0–155.0 days) and an OS of 367 days (95% CI: 310.4–420.6 days) in patients with mCRC (10). The above findings suggest that treatments based on chemotherapeutic agents and targeted antiangiogenic drugs can potentially be late-line therapies for mCRC.

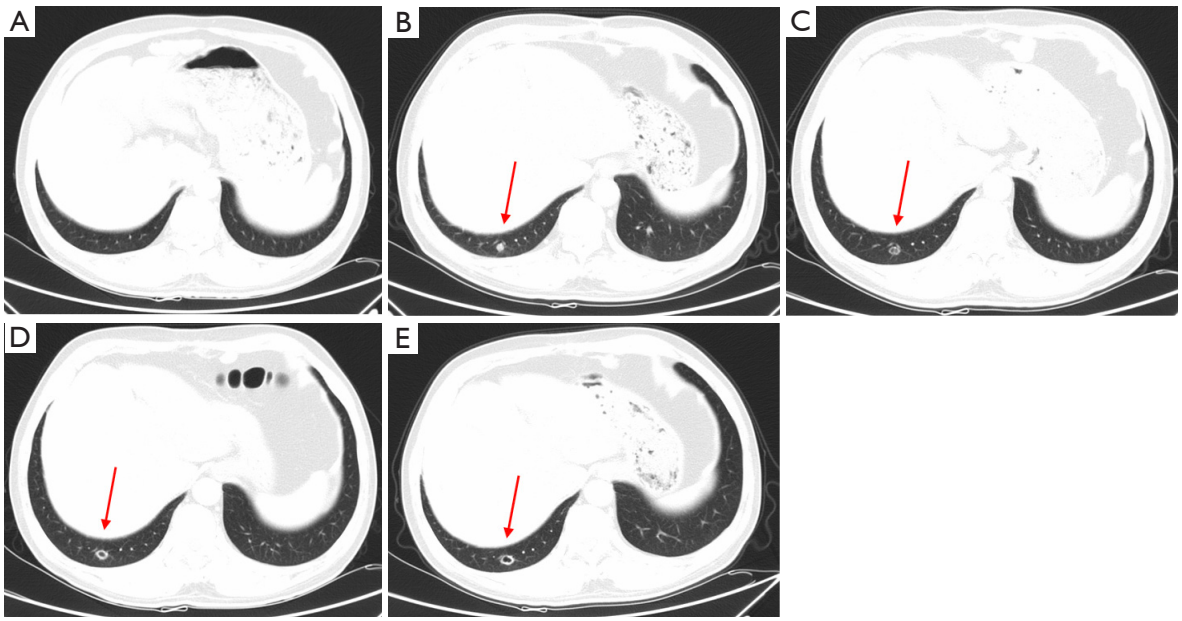

Figure 4 CT images of the lungs. (A) CT on September 27, 2020, demonstrated that no lesion existed in the right lung. (B) CT on January 18, 2021, showed that new lung lesions had developed in the lower lobe of the right lung (red arrow) after chemotherapy had been discontinued for 2 months. (C) CT on April 26, 2021, demonstrated hollowing of the lesion in the lower lobe of the right lung (red arrow) after continued therapy. (D) CT on August 12, 2021, showed that the cavitation of the lesion in the right lower lung was enlarged (red arrow). (E) CT on November 15, 2021, showed no obvious change in the cavitation of the lesion in the right lower lung (red arrow) compared with that in August 2021. CT, computed tomography.

Systemic chemotherapy can downregulate VEGF-A and VEGF-C (13). The currently used VEGF inhibitors, such as bevacizumab, inhibit the VEGF-A/VEGFR pathway and angiogenesis. Several phase II clinical trials have supported the combined use of an antiepidermal growth factor receptor agent and an antiangiogenic drug as a late-line treatment for mCRC, including the BOND-2 trial (cetuximab, bevacizumab and irinotecan) (14) and 2 studies by Chen *et al.* published in 2019 (S-1 and raltitrexed) (9) and 2021 (S-1, raltitrexed and bevacizumab) (10). However, the phase III PACCE trial (oxaliplatin or irinotecan plus bevacizumab with or without panitumumab) showed no benefit of the combination (15). Further, the phase III CAIRO2 trial (bevacizumab and capecitabine/oxaliplatin with or without cetuximab) suggested a shortening of PFS in patients who received bevacizumab and cetuximab (16). Hence, the response of mCRC to late-line treatment likely depends on the combination of agents used, highlighting the need for additional research to establish optimal drug combinations.

The effects of VEGF inhibitors on VEGF-C-induced lymphangiogenesis are limited. Fruquintinib inhibits VEGFR-1, -2, and -3 and suppresses all VEGFR-dependent pathways, including tumor angiogenesis and lymphangiogenesis (17). Therefore, we speculated that the combination of fruquintinib, S-1, and raltitrexed might exert strong antitumor effects. The patient described in this case report exhibited a PR to treatment with this combination of drugs that allowed him to meet the indications for surgery and achieve a long PFS. The potential benefits of fruquintinib-based combination therapies are supported by another case report describing a patient with mCRC who was successfully treated with cetuximab and fruquintinib (18). Nevertheless, the patient in the present study developed lung metastases during treatment. We speculate that pulmonary metastasis may have occurred following the temporary discontinuation of the fruquintinib-based therapy from October 2019 to February 2020 due to liver surgery.

The patient described here was diagnosed with Hodgkin lymphoma in addition to mCRC. Reports of patients with simultaneous solid and hematologic primary malignancies

are uncommon. Diagnosis of the patient's malignancies, evaluation of the patient's clinical condition, and selection of the therapeutic regimens after weighing up the possible advantages and disadvantages necessitated close cooperation and detailed discussions between members of a multidisciplinary team that included physicians from the Hematology Department. The lymphoma was considered a treatment priority for this patient because the tumor burden and the Ki67 index were high. Furthermore, it was considered that treatment of the lymphoma would control its clinical manifestations, such as dizziness, exhaustion, and fever. In addition, chemotherapy can potentially cure early-stage lymphoma. Therefore, the multidisciplinary team made the decision to discontinue the chemotherapy for CRC and administer 4 cycles of antilymphoma chemotherapy based on the ABVD regimen. This approach successfully controlled the lymphoma without preventing subsequent treatment of the mCRC from achieving good efficacy.

Conclusions

In conclusion, this report describes a rare case of a patient with mCRC who also developed Hodgkin lymphoma. Successful management of both primary malignancies required close cooperation between a multidisciplinary team. Importantly, third-line treatment of the mCRC with a combination of fruquintinib, raltitrexed, and S1 achieved a PR that enabled the patient to undergo surgery for liver metastasis. The findings suggest that regimens based on this drug combination might be clinically effective as late-line therapy for mCRC, although this will need to be confirmed by clinical trials.

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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-23-39/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-39/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-39/coif). The 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 Declaration of Helsinki (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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