Efficacy of sintilimab and fruquintinib combination treatment in the management of microsatellite-stable metastatic colorectal cancer: a case report

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Background: The immune microenvironment of deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H) colorectal cancer exhibits better immune activity, and patients with dMMR/MSI-H colorectal cancer benefit from immunotherapy with programmed death-1 (PD-1)/PD-1 ligand (PD-L1) inhibitors and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors as a first-line treatment. However, for microsatellite-stable (MSS) colorectal cancer, which accounts for the majority of the cases of colorectal cancer, immunotherapy has yielded little success, especially in cases of patients with advanced colorectal cancer in whom multiple lines of chemotherapy have failed. Hence, safe and effective targeted treatment strategies are urgently needed to achieve greater survival benefits.

Case Description: We report a case in which next-generation sequencing (NGS) and immunohistochemistry (IHC) showed that that the patient's molecular characteristics were as follows: MSS, low expression of PD-L1, and high tumor mutation burden (TMB-H). Due to the failure of multiple lines of chemotherapy and severe chemotherapeutic adverse effects, a combined targeted immunotherapy regimen was utilized. After 6 months of treatment, imaging suggested near-complete clinical remission, and at the 18-month follow-up, the patient had a good quality of life and imaging showed no tumor recurrence.

Conclusions: This case suggests that a good response to a combined targeted immunotherapy regimen can be achieved in patients with MSS metastatic colorectal cancer, in addition, it also suggests that TMB-H is a predictive biomarker for clinical benefit from immunotherapy in MSS metastatic colorectal cancer.

Keywords: Programmed death-1 inhibitor (PD-1 inhibitor); vascular endothelial growth factor receptor inhibitor (VEGFR inhibitor); tumor mutation burden (TMB); microsatellite-stable (MSS); case report

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Introduction

Immune checkpoint blockade therapy is currently the most popular tumor immunotherapy, with the most widely used and studied immune checkpoint inhibitors (ICIs) being programmed death-1 (PD-1)/PD-1 ligand (PD-L1) inhibitors. These inhibitors have been successfully used in the treatment of most solid tumors. Currently, the biomarkers for predicting the response of PD-1/PD-L1 immunotherapy include PD-L1, deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H), and tumor mutation burden (TMB), of which high TMB (TMB-H, i.e., TMB >10 mut/Mb) was approved by the Food and Drug Administration (FDA) in 2020 as a biomarker for response to the PD-1 inhibitor, pablizumab, in the treatment of solid tumors (1). In the Keynote 158 trial, TMB emerged as a second pan-cancer

immunotherapy biomarker. According to the response rate to ICI therapy among different tumor types, researchers have classified tumors into "cold", "hot", "excluded", and "immunosuppressed" tumors. Colorectal cancer, which has shown a low response rate to ICI therapy, is considered a "cold" tumor (2). At present, the National Comprehensive Cancer Network (NCCN) guidelines only recommend pembrolizumab monotherapy or nivolumab in combination with ipilimumab as a treatment for dMMR/MSI-H metastatic colorectal cancer. dMMR/MSI-H colorectal cancer represent 5% of all metastatic colorectal cancer cases and are characterized by TMB-H and high immune infiltration compared with microsatellite-stable (MSS) colorectal cancer (3). However, it has been shown that a small proportion of patients with MSS metastatic colorectal cancer continue to exhibit TMB-H despite therapy (4). In these patients, the response to ICI treatment remains unclear. We also don't know whether TMB-H can be used as a good predictor of the clinical benefit of MSS metastatic colorectal cancer.

Sintilimab is a type of PD-1 inhibitors, has been approved for first-line treatment of patients with advanced-stage or inoperable hepatocellular carcinoma (HCC), squamous cell cancer and non-squamous non-small cell lung cancer (NSCLC) in China. Fruquintinib belongs to tyrosine kinase inhibitors, which acts as a highly selective inhibitor for all types of vascular endothelial growth factor (VEGFR) receptors, including VEGFR1, VEGFR2, and VEGFR3, has been approved for third-line or later treatment of patients with metastatic colorectal cancer in China.

Herein, we report the case of a 64-year-old woman with metastatic colorectal cancer who showed microsatellite stability but TMB-H in response to the PD-1 inhibitor, sintilimab, used in combination with the VEGFR inhibitor, fruquintinib, and report the preliminary results. In this case, although there is no definite evidence, it is also tentatively suggested that TMB-H might be able to act as a good predictor of clinical benefit. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-359/rc).

Case presentation

A 64-year-old woman was hospitalized for abdominal pain and blood and mucus in the stool in the First Affiliated Hospital of Guangzhou University of Chinese Medicine in September 2007, and underwent laparoscopic left hemicolectomy in December 2007. Her postoperative pathological examination of the left hemi-colon suggested moderately differentiated adenocarcinoma (pT3N2bM0, stage IIIC). From September 2007 to February 2008, the patient underwent six cycles of adjuvant chemotherapy (three cycles each of FOLFOX and XELOX regimens), followed by surgery. Computed tomography (CT) performed in July 2009 showed right parametrial occupancy, which was considered indicative of metastasis. The patient subsequently underwent a comprehensive staging procedure laparoscopically for ovarian cancer in November 2009. Her postoperative pathological examination suggested the following: moderately to poorly differentiated adenocarcinoma of the right ovary, right broad ligament, and peritoneum. This finding, combined with clinical and immunohistochemistry (IHC) results, was considered indicative of gastrointestinal adenocarcinoma metastasis. There were no signs of cancer in the other tissues or lymph nodes. The patient then underwent four cycles of chemotherapy (TC regimen) from November 2009 to January 2010. A repeat positron emission tomography (PET)-CT was performed in October 2014, which revealed a hypermetabolic lesion in the left iliac fossa, which was considered to be a metastatic tumor. Histopathology of the punctured mass showed infiltration of a moderately to poorly differentiated adenocarcinoma. The patient then underwent two cycles of chemotherapy with the FOLFOX regimen, followed by concurrent chemoradiotherapy (one cycle of the XELOX regimen and capecitabine monotherapy). Repeat pelvic magnetic resonance imaging (MRI) upon completion of radiotherapy showed that the tumor beside the external iliac vessels had completely disappeared, indicating a complete response. Follow-up examinations until October 2019, during which time CT was repeated regularly, suggested no recurrence of pelvic tumors (*Figure 1A*). Reviews of thoracic CT scans in August 2019 and October 2019 suggested persistent clinical remission of the left upper lung lesion (*Figure 1B*). The patient had a good quality of life through immunotherapy at the follow-up until September 2021, with a review of chest radiography showing mostly normal findings (*Figure 1C*).

A review of thoracic CT findings in December 2018 suggested mass or nodular shadows in the anterior segment of the left lung and multiple lymphadenomegaly in the mediastinum and left hilar region; thus, the possibility of a tumor could not be excluded. PET-CT suggested that the left upper lung lesion was malignant. Multiple lymph nodes metastases were

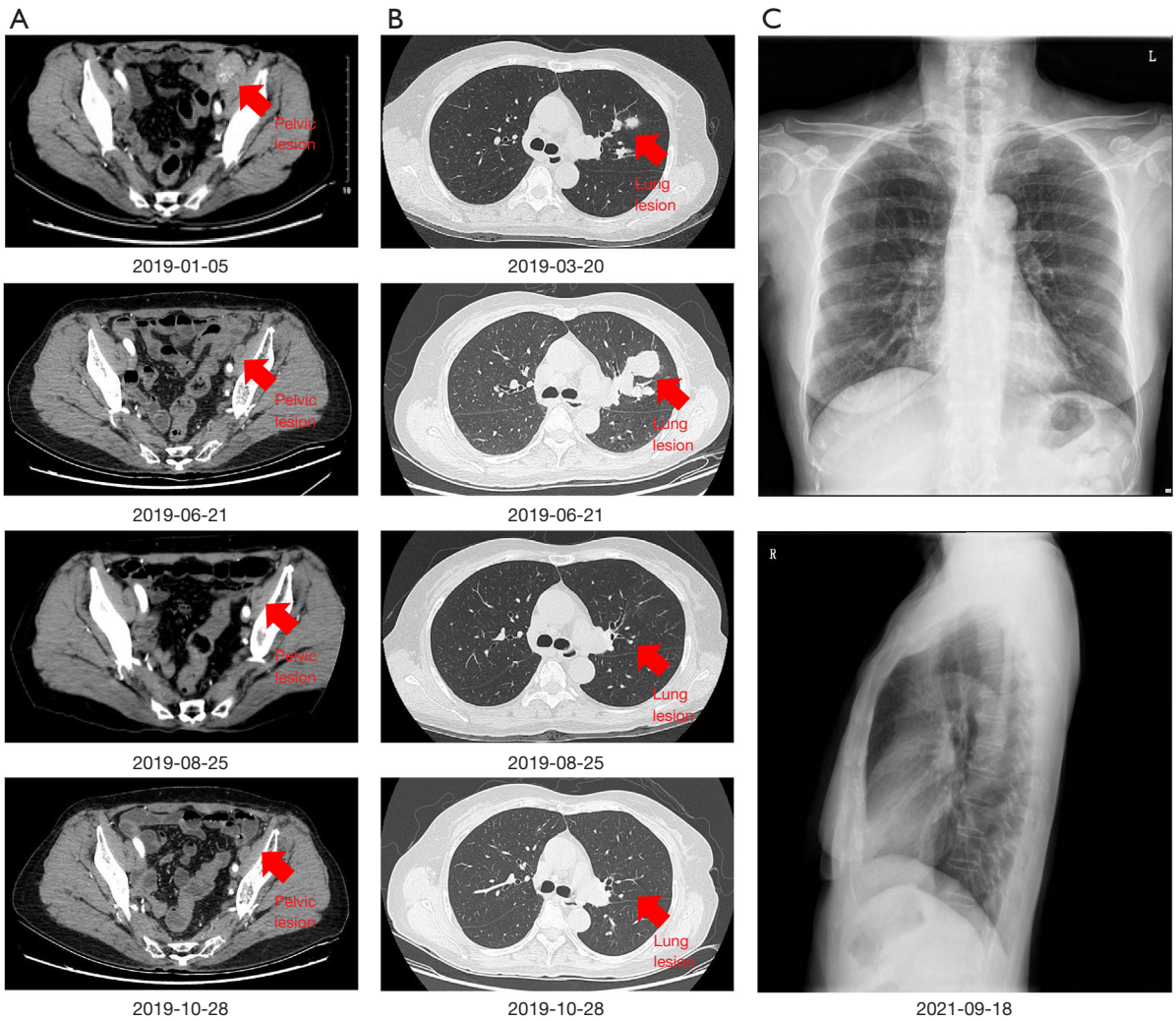

Figure 1 Imaging findings of the patient. (A) Pelvic CT scan: lymphatic metastases around the left external iliac artery, the red arrows indicate the lesion. (B) Thoracic CT scan: the left upper lung lesion and multiple lymphadenomegaly in the mediastinum and left hilar, the red arrows indicate the lesion. (C) Chest radiography suggesting approximately normal findings. CT, computed tomography.

noted in the left supraclavicular, left hilar, mediastinal, and retroperitoneal regions along with suspected adrenal metastases. Bronchoscopic biopsy (*Figure 2A,2B*) performed in December 2018 suggested metastatic intestinal adenocarcinoma. Immunohistochemical staining results were as follows: CK7, negative; CK20, partially positive; TTF-1, negative; Napsin A, negative; CDX-2, partially positive; and villin, positive. One cycle of the FOLFOXIRI regimen was administered in January 2019, and the chemotherapy regimen was changed to cetuximab combined with irinotecan due to IV degree myelosuppression. Treatment response of the left upper lung lesion was evaluated as a progressive disease (PD) after five cycles of chemotherapy, after which the patient declined chemotherapy. To determine the next treatment option, biopsy tissues obtained in December 2018 were subjected to IHC and next-generation sequencing (NGS) test, the PD-L1 IHC suggested that PD-L1 expression was 1% (*Figure 2C*), and the NGS findings were as follows: microsatellite stability (*Figure 3A*), TMB-H (14.52 mut/Mb, *Figure 3B*), wild-type *NRAS/KRAS/BRAF* expression, and *TP53* mutation. As NGS suggested a TMB-H status, immunotherapy was considered potentially effective. After obtaining informed consent, the patient was treated with six cycles of treatment with the PD-1 inhibitor, sintilimab, from June 2019 to October 2019; in four of the cycles, the VEGFR inhibitor, fruquintinib, was administered in combination with

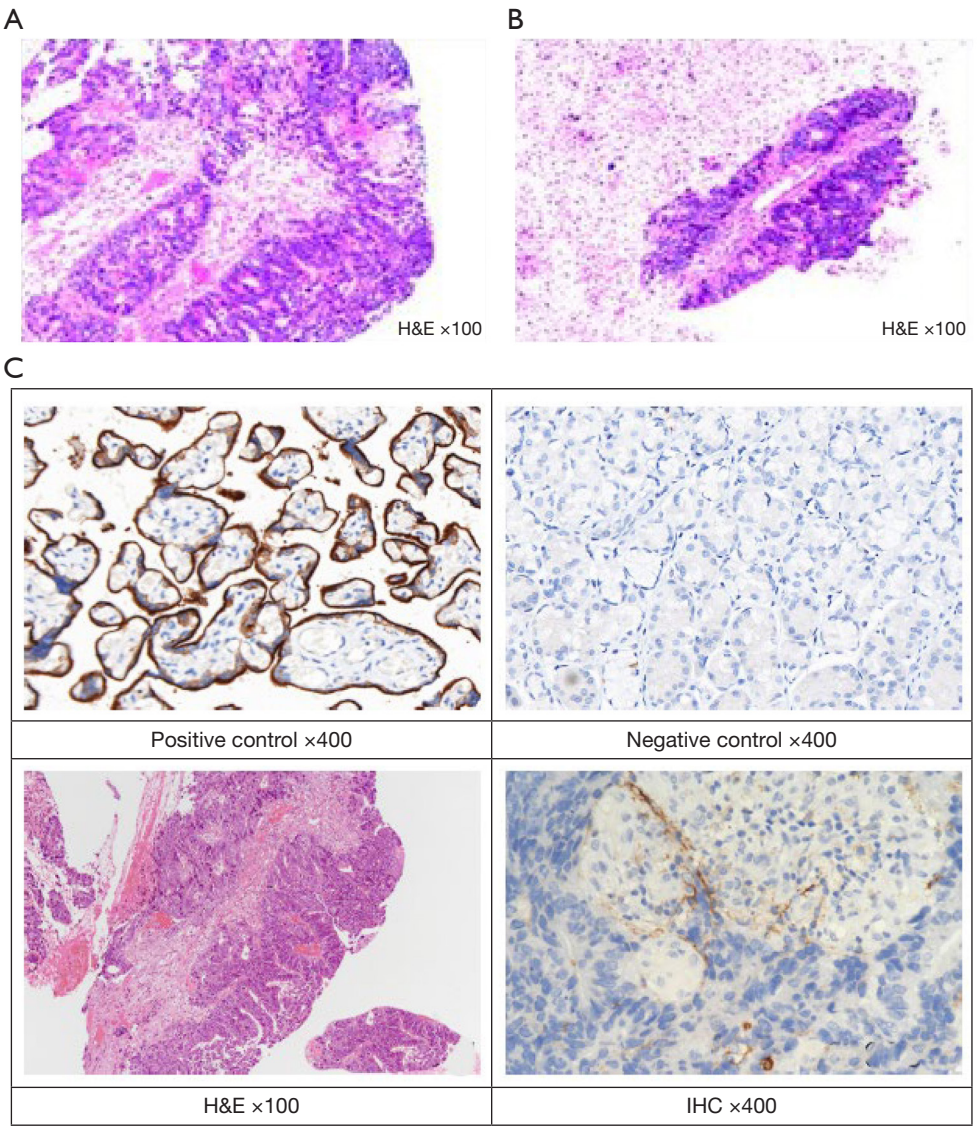

Figure 2 Pathological morphology features and IHC results of the patient. (A) The left upper lung lesion biopsy result is metastatic intestine adenocarcinoma. H&E staining, ×100. (B) The hilar lymph node biopsy result is metastatic intestine adenocarcinoma. H&E staining, ×100. (C) The left upper lung lesion PD-L1 IHC suggested that PD-L1 expression is 1%. PD-L1 IHC staining, ×400. Positive control means PD-L1 positive IHC staining in tumor cells; negative control means PD-L1 negative IHC staining in tumor cells. H&E, hematoxylin and eosin; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

sintilimab. Due to grade 2 hand-foot skin reaction and hoarseness after taking fruquintinib, the patient voluntarily stopped the drug in October 2019 and continued immunotherapy with sintilimab alone until January 2020, and eventually chose to discontinue immunotherapy for financial reasons, having received a total of 10 cycles of immunotherapy. She continued traditional Chinese medicine (TCM) therapy after stopping immunotherapy, and her last follow - up examination was performed in September 2021. *Figure 4* shows the diagnosis and treatment administered in this case.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from this patient for publication of this case

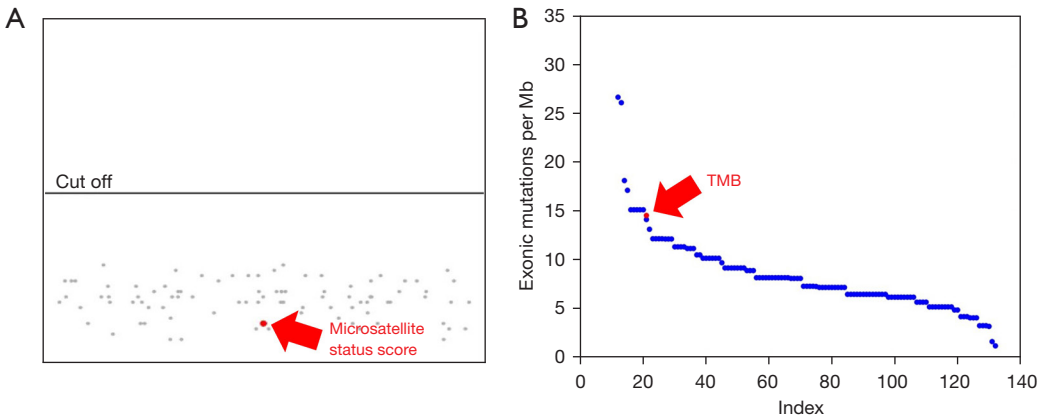

Figure 3 The NGS testing result of microsatellite status and TMB. (A) The microsatellite status result shows MSS (MSI status by MSIsensor based on NGS), the red arrow indicates the microsatellite status score. (B) The TMB analysis reveals TMB-H (higher than 85% of colon cancers, by NGS), the red arrow indicates the exonic mutations per Mb. TMB, tumor mutation burden; NGS, next-generation sequencing. MSS, microsatellite-stable; MSI, microsatellite instability; TMB-H, high TMB.

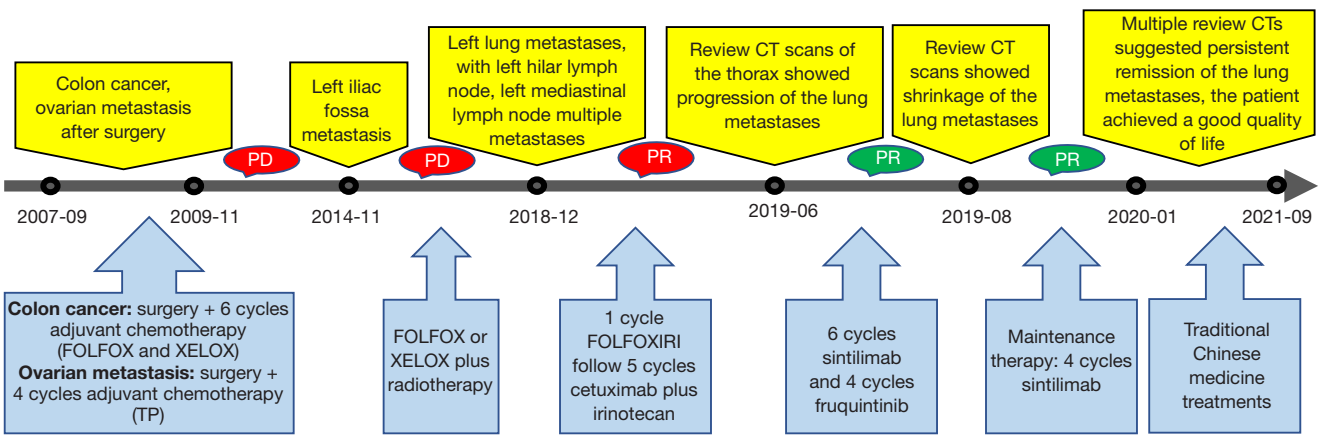

Figure 4 Flow of diagnosis and treatment. CT, computed tomography; PD, progressive disease; PR, partial response; TP, Taxol (paclitaxel)-Platinum (cisplatin/carboplatin) regimen.

report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Immune checkpoint blockade therapy has achieved excellent results in the treatment of dMMR/MSI-H colorectal cancer, and the results of three large multicenter studies, including Keynote-164, Keynote-177, and Checkmate-142 (5-7), have confirmed that PD-1/PD-L1 inhibitors or cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors can achieve better clinical benefits compared to single-agent chemotherapy or chemotherapy combined with targeted therapy. However, dMMR/MSI-H colorectal cancer represent 5% of all metastatic colorectal cancer cases (3), with most patients showing a microsatellite-steady state. The reduced infiltration of immune cells within the immune microenvironment of MSS colorectal cancer, especially the reduced infiltration of $CD8^+$ T-cells (8), which play a major role in killing tumor cells, also reduces the response rate to immunotherapy. Therefore, improvement of the response rate to immunotherapy in MSS colorectal cancer has become an urgent issue related to the use of

immunotherapy in colorectal cancer treatment.

Currently, the FDA has approved TMB-H (TMB >10 mut/Mb) as a biomarker for pembrolizumab in the treatment of solid tumors. The key factor underlying the use of TMB-H as an efficacy prognostic indicator for ICIs is that TMB can indirectly reflect the ability to produce neoantigens in solid tumors (9,10). Since mutated tumor genes can produce new proteins, the degradation products of these proteins are presented by major histocompatibility complex to form neoantigens on the surface of tumor cells. These are then recognized by activated $CD8^+$ T cells, thereby triggering an immune response targeting tumor cells and altering the immune microenvironment of the tumor tissue (11), and ultimately allowing ICIs to take effect. A meta-analysis based on 117 clinical studies (12) showed that in most solid tumors, higher TMB was associated with better efficacy of ICI treatment. TMB has been confirmed as an independent predictor of treatment efficacy for ICIs (13,14), with almost all dMMR/MSI-H colorectal cancers and even some MSS colorectal cancers exhibiting TMB-H. One study that included 6,004 cases of colorectal cancer (4) showed that a total of 302 cases (5%) exhibited MSI-H, of which 301 showed TMB-H, and another 164 of 5,702 cases that exhibited microsatellite stability still exhibited TMB-H. Therefore, in this case, based on the above findings, the combination of the PD-1 inhibitor, sintilimab, with the VEGFR inhibitor, fruquintinib, was chosen to treat the patient in the event of failure of multiple lines of chemotherapy, and excellent efficacy was achieved.

However, many questions regarding the treatment of this case remain unresolved. A crucial point is whether the threshold for using TMB-H as a predictor of treatment with ICIs should be higher for colorectal cancer without immune infiltration in the MSS state compared with other solid tumors. In this case, the TMB was 14.52 mut/Mb, which meets the FDA definition of TMB-H for solid tumors based on the Keynote-158 study (15). That study included anal squamous cell carcinomas, biliary adenocarcinomas, well and moderately differentiated neuroendocrine tumors, endometrial carcinomas, cervical squamous cell carcinomas, vulvar squamous cell carcinomas, small-cell lung carcinomas, malignant pleural mesotheliomas, papillary or follicular thyroid carcinomas, salivary gland carcinomas, and any other advanced solid tumor (except colorectal cancer) with MSI-H, and thus, the results were not fully applicable to MSS colorectal cancer in terms of the experimental design. Clinical practice studies have shown major differences in the TMB threshold criteria between cancer types, and their findings suggest that differences in panels, detection platforms, bioinformatics analysis methods, and other factors may have a major impact on the TMB threshold (16). One study by Samstein *et al.* confirmed (14) that the TMB threshold for immunotherapy benefit varies across cancer types. In studies of different cancer types based on tests performed by Foundation One, the TMB threshold for benefit from treatment with atezolizumab in bladder cancer (17) was 16 mut/Mb, and that for NSCLC (18) was 13.5 mut/Mb in first-line treatment and 17.1 mut/Mb in second-line treatment. For NSCLC, small-cell lung cancer (SCLC), and melanoma, the TMB thresholds were 307, 248, and 100 mut/Mb, respectively, based on whole-exome sequencing (WES) detection (19-21). Meanwhile in colorectal cancer, the TMB-H thresholds obtained from different studies fluctuated between 10 and 41 mut/Mb (4,9,22). Since the interpretation criteria of dMMR/MSI-H are widely accepted worldwide and the threshold of TMB-H remains debatable due to the discrepant factors described above, the generalized use of TMB >10 mut/Mb as an indicator of pan-cancer immunotherapy benefit will cause much confusion in clinical practice, and the TMB-H threshold should be based on different cancer types for further clarification.

On the other hand, while the treatment strategy of ICI therapy combined with VEGFR-targeted therapy achieved excellent clinical efficacy in this case, targeted therapy may still play a critical role in reversing the immunosuppressive microenvironment of MSS colorectal cancer, inducing the development of immune microenvironment characteristics similar to those of dMMR/MSI-H colorectal cancer, thereby allowing patients to benefit from ICI therapy. VEGFR inhibitors can play an effective role in the tumor microenvironment, not only in normalizing tumor vasculature, but also in enhancing the infiltration of immunologically active cells such as $CD8^+$ T cells (23,24), which can improve clinical efficacy when combined with PD-1/PD-L1 inhibitor therapy; several studies involving HCC and melanoma (25-27) have confirmed these ideas. In the REGONIVO study (28), treatment with regorafenib combined with nivolumab for patients with advanced MSS colorectal cancer who had failed multiple chemotherapy treatments yielded an objective response rate (ORR) of 36% and a median progression-free survival (mPFS) of 7.9 months. In another exploratory study of camrelizumab combined with apatinib for MSS metastatic colorectal cancer, some patients also achieved stable disease (SD) (29).

In 2021, American Society of Clinical Oncology (ASCO) published a phase Ib study of fruquintinib in combination with sintilimab for metastatic colorectal cancer (abstract 2514) (30), with preliminary results showing an overall ORR of 22.7% and a disease control rate (DCR) of 86.4%. For all 44 patients enrolled, the mPFS was 5.6 months, and the median overall survival (mOS) was 11.8 months. However, the study has not yet published the results of the subgroup analysis based on microsatellite status, and it still deserves further attention (30). Although published evidence suggesting a synergistic effect of immunotherapy combined with targeted therapy in MSS colorectal cancer is limited, it can still be used to propose new treatment strategies and research directions for the treatment of MSS colorectal cancer. As in the present case, many questions remain that deserve further exploration, and resolving these questions may provide more hope for the treatment of MSS colorectal cancer that has failed multiple lines of chemotherapy or shown intolerance to chemotherapy. Combining both economic and efficacy aspects, the regimen of sintilimab combined with fruquintinib is more applicable in China. In the context of our case report, we believe that this treatment option deserves to be considered for refractory metastatic colorectal cancer that has failed multiple lines of chemotherapy, regardless of MSI status, as long as NGS testing suggests TMB-H, with the aim of achieving good clinical outcomes.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-359/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-359/coif). All authors report support from 3D Medicines Inc for providing the next-generation sequencing (NGS). Dr. MJ reports funding support from the Teaching Reform Project of the Department of Education of Guangdong Province of China (No. 2020138). The authors have no other 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 national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from this 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.

References

1. U.S. Food & Drug Administration. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. [2020-07-17]. Available online: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors
2. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 2019;18:197-218.
3. Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015;5:43-51.
4. Fabrizio DA, George TJ Jr, Dunne RF, et al. Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. J Gastrointest

Oncol 2018;9:610-7.
5. Le DT, Kim TW, Van Cutsem E, et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. J Clin Oncol 2020;38:11-9.
6. Andre T, Amonkar M, Norquist JM, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:665-77.
7. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
8. Mlecnik B, Bindea G, Angell HK, et al. Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability. Immunity 2016;44:698-711.
9. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.
10. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69-74.
11. Fumet JD, Truntzer C, Yarchoan M, et al. Tumour mutational burden as a biomarker for immunotherapy: Current data and emerging concepts. Eur J Cancer 2020;131:40-50.
12. Osipov A, Lim SJ, Popovic A, et al. Tumor Mutational Burden, Toxicity, and Response of Immune Checkpoint Inhibitors Targeting PD(L)1, CTLA-4, and Combination: A Meta-regression Analysis. Clin Cancer Res 2020;26:4842-51.
13. Goodman AM, Kato S, Bazhenova L, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther 2017;16:2598-608.
14. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet 2019;51:202-6.
15. Yap TA, Nakagawa K, Fujimoto N, et al. Efficacy and safety of pembrolizumab in patients with advanced mesothelioma in the open-label, single-arm, phase 2 KEYNOTE-158 study. Lancet Respir Med 2021;9:613-21.
16. Büttner R, Longshore JW, López-Ríos F, et al. Implementing TMB measurement in clinical practice: considerations on assay requirements. ESMO Open 2019;4:e000442.
17. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67-76.
18. Marcin K, Wei Z, Shames D. Tumor mutation burden (TMB) is associated with improved efficacy of atezolizumab in 1L and 2L+ NSCLC patients. J Thorac Oncol 2016;4:abstr OA20.01.
19. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer. Cancer Cell 2018;33:843-52.e4.
20. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell 2018;33:853-61.e4.
21. Riaz N, Havel JJ, Makarov V, et al. Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. Cell 2017;171:934-49.e16.
22. Schrock AB, Ouyang C, Sandhu J, et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol 2019;30:1096-103.
23. Schmittnaegel M, Rigamonti N, Kadioglu E, et al. Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. Sci Transl Med 2017;9:eaak9670.
24. Allen E, Jabouille A, Rivera LB, et al. Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation. Sci Transl Med 2017;9:eaak9679.
25. Hack SP, Spahn J, Chen M, et al. IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation. Future Oncol 2020;16:975-89. Erratum in: Future Oncol 2020;16:2371.
26. McDermott DF, Huseni MA, Atkins MB, et al. Publisher Correction: Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med 2018;24:1941.
27. Hodi FS, Lawrence D, Lezcano C, et al. Bevacizumab plus ipilimumab in patients with metastatic melanoma. Cancer Immunol Res 2014;2:632-42.
28. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib

Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). J Clin Oncol 2020;38:2053-61.
29. Ren C, Mai ZJ, Jin Y, et al. Anti-PD-1 antibody SHR-1210 plus apatinib for metastatic colorectal cancer: a prospective, single-arm, open-label, phase II trial. Am J Cancer Res 2020;10:2946-54.
30. Guo Y, Zhang W, Ying J, et al. Preliminary results of a phase 1b study of fruquintinib plus sintilimab in advanced colorectal cancer. J Clin Oncol 2021;39:abstr 2514.

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