Case Report

Partial response to crizotinib + regorafenib + PD-1 inhibitor in a metastatic *BRAF* V600EMT colon cancer patient with acquired *C-MET* amplification and *TPM4-ALK* fusion: a case report

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Background: Colorectal cancer (CRC) with the Raf murine sarcoma viral oncogene homolog B (*BRAF*) V600E had a relatively poor prognosis. Anaplastic lymphoma kinase (*ALK*) fusion and the mesenchymal-to-epithelial transition factor (*MET*) amplification have been recognized as potentially important therapeutic targets in non-small cell lung cancer (NSCLC). However, both of them are of extremely lower frequencies (<2%) in metastatic CRC, and few studies have mentioned the real application of their inhibitors in CRC treatment.

Case Description: A 49-year-old Chinese male was diagnosed with ascending colon adenocarcinoma (cT3N+?M1) with liver metastases. The patient performed next-generation sequencing (NGS) using tissue and circulating tumor DNA (ctDNA), and the results showed a *BRAF* V600E mutation. He received an initial combination treatment with cetuximab, dabrafenib, and trametinib with a partial response (PR) assessment. We changed the therapy regimen on this patient several times because of the patient's intolerance to the drugs or the inefficacy of the treatment. During this period, we detected the c-MET amplification and tropomyosin 4 (*TPM4*)-*ALK* fusion by NGS after triplet targeted therapy (tislelizumab, dabrafenib, and trametinib), thus he was finally treated with programmed cell death protein 1 (PD-1) inhibitor (tislelizumab), MET/ALK inhibitor (crizotinib) plus multikinase inhibitor (regorafenib). Imageological examinations showed that PR was achieved and ctDNA sequencing results indicated a significantly reduced *BRAF* mutation frequency, *MET* amplification and *TPM4-ALK* fusion were undetectable. NGS analysis of peripheral blood showed a recurrence of the *MET* acquired resistant amplification mutation over 2 months of ongoing treatment. but the patient was assessed as PR and still under treatment of crizotinib, tislelizumab and regorafenib within good physical condition. At the last follow-up on October 2021, the patient died of symptomatic treatment fail for obstructive jaundice. The patient finally achieved 11 months overall survival.

Conclusions: This study reported a co-existence of a *BRAF* V600E mutation, *c-MET* amplification and *TPM4-ALK* fusion in a CRC patient. Administration of crizotinib combined with regorafenib and tislelizumab obtained an obvious response. Furthermore, continuous ctDNA detection appears to be a promising technique to monitor tumor burden, which may provide better clinical decision support during the disease course.

Keywords: Case report; colorectal cancer (CRC); *BRAF* V600E; programmed cell death protein 1 (PD-1); circulating tumor DNA monitoring (ctDNA monitoring)

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Introduction

Colorectal cancer (CRC) is among the most lethal and prevalent malignancies in the world and its incidence continues to rise among patients aged 40–49 (1). Advances in novel therapy development and scientific drug regimen design have significantly prolonged the survival of patients with CRC. However, these are far from meeting the urgent needs in clinics (2-4).

The Raf murine sarcoma viral oncogene homolog B (*BRAF*) mutation is detected in 8–10% of metastatic CRCs (mCRCs) and is strongly correlated with patients' poor prognosis (5,6). It was reported that patients with *BRAF* V600E mutation showed a poor outcome than those with non-V600E mutations (7). Recently, studies on therapies for *BRAF*-mutated mCRC patients have obtained several advances. The BEACON subgroup analysis showed patients who received doublet (encorafenib plus cetuximab) therapies showed improved median overall survival (OS) compared with the patients treated with FOLFOXIRI regimen (fluorouracil, folic acid and irinotecan) (8). Based on this, the Food and Drug Administration (FDA) approved doublet regimen for mCRC patients with *BRAF* V600E mutation after first-line therapy (9).

Anaplastic lymphoma kinase (*ALK*) has been found fused to various genes in diverse cancers (10) and a variety of *ALK* fusions resulting in constitutive activation of *ALK* have been identified in human cancers (11). Mesenchymal-to-epithelial transition factor (*MET*) is the tyrosine kinase receptor for hepatocyte growth factor, and more recently, activating mutations and copy number amplification in *MET* have been recognized as potentially important therapeutic targets in non-small cell lung cancer (NSCLC) (12-14). However, both *MET* amplification and tropomyosin 4 (*TPM4*)-*ALK* fusion are of extremely lower frequencies (<2%) in mCRC, and few studies have described them as an acquired mutation (15,16). Not to mention the real application of their inhibitors in CRC treatment.

In this study, we identified a rarely reported *TPM4*-*ALK* fusion co-occurring with *MET* amplification in a CRC patient with *BRAF* V600E mutation who achieved partial response (PR) after the combined therapy of programmed cell death protein 1 (PD-1) inhibitor (tislelizumab), MET/ALK inhibitor (crizotinib) plus multikinase inhibitor (regorafenib), and whose response was monitored by continuous ctDNA detection. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-155/rc).

Highlight box

Key findings

- A rarely case of tropomyosin 4 (*TPM4*)-anaplastic lymphoma kinase (*ALK*) fusion co-occurring with mesenchymal-to-epithelial transition factor (*MET*) amplification in a colorectal cancer (CRC) patient with the Raf murine sarcoma viral oncogene homolog B (*BRAF*) V600E mutation who achieved partial response (PR) after the combined therapy of programmed cell death protein 1 (PD-1) inhibitor (tislelizumab), MET/ALK inhibitor (crizotinib) plus multikinase inhibitor (regorafenib), and whose response was monitored by continuous circulating tumor DNA (ctDNA) detection.

What is known and what is new?

- *BRAF* V600E mutation showed a poor outcome than those with non-V600E mutations.
- FDA approved doublet regimen for metastatic CRC (mCRC) patients with *BRAF* V600E mutation after first-line therapy, but not to mention the real application of *ALK* fusion inhibitor in CRC treatment.
- Liquid biopsy may help clinicians to tailor treatment and forecast patient prognosis, especial for tissue size may not be enough to conduct next-generation sequencing.

What is the implication, and what should change now?

- A novel combination of crizotinib, tislelizumab and regorafenib is a more effective and safer option for co-existence *BRAF* V600E, *c-MET* amplification and *ALK* fusion co-existence patient.
- CtDNA monitor is indispensable during the treatment of mCRC patients and can be served as a promising tool during their follow-up.

Case presentation

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 the 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.

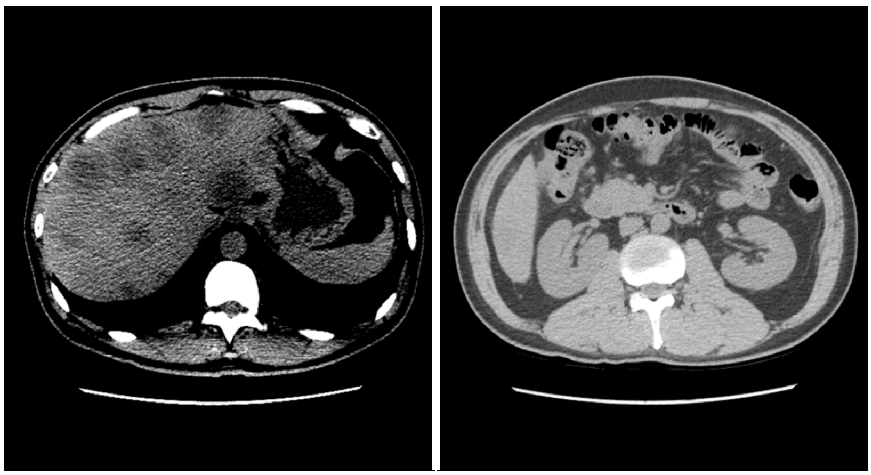

Figure 1 Computed tomography (left) and magnetic resonance imaging (right) scans confirmed baseline colorectal cancer synchronous liver metastasis.

A 49-year-old Chinese male with right upper abdominal pain for more than 6 months was admitted to Beijing Hospital (Beijing, China) on October 10, 2020. Laboratory examination indicated the serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125) and alpha-fetoprotein was 46.3 ng/mL, >12,000 U/mL, 932.6 U/mL and 3 ng/mL, respectively. The colonoscopy showed a tumor (mass) located at the hepatic flexure. There was stenosis but no obstruction. The computed tomography (CT) and magnetic resonance imaging (MRI) results exhibited that there were more than 30 unresectable liver metastases (*Figure 1*). From the biopsy, the histopathological and molecular diagnosis suggested low-grade poorly differentiated adenocarcinoma with a *BRAF* V600E mutation but wild type kirsten rat sarcoma viral oncogene homologue (*KRAS*), neuroblastoma-RAS (*NRAS*), and phosphoinositide 3-kinase alpha (*PIK3CA*). The patient did not harbor erb-b2 receptor tyrosine kinase 2 (*HER2*) amplification, and PD-1/programmed cell death ligand 1 (PD-L1) staining showed negative. We finally diagnosed the patient as colon adenocarcinoma with liver metastases according to the National Comprehensive Cancer Network (NCCN) 2021 guideline for colon cancer (17). The tumors were unresectable with clinical risk score (CRS) of 4. The stage of the tumor was cT3N+?M1. The patient's tissue and blood samples were subjected to next-generation sequencing (NGS), and the results showed the presence of *BRAF* V600E mutation with a mutant allele frequency of 27.92% (*Figure 2*). The abdominal pain exacerbated so rapidly within 10 days that the patient could not stand up, necessitating an urgent treatment.

The patient received a series of treatments as shown in *Figure 2*. Considering the rapid progression of the tumor and worsening of liver function, he first received a combination therapy of triplet targeted agents: an epidermal growth factor receptor (*EGFR*) inhibitor, cetuximab (500 mg/m^2), a *BRAF* inhibitor, dabrafenib (150 mg, BID), and a mitogen-activated protein kinase kinase 1 (*MEK*) inhibitor, trametinib (2 mg, QD) for six cycles. It achieved a satisfactory efficacy with a dramatic decrease of bilirubin, CEA, CA19-9 and CA125. On December 4, 2020, the patient's blood sample was sent for NGS again, which showed that *BRAF* V600E mutation frequency was significantly reduced to 3.2% (*Figure 2*). Subsequent MRI examination showed that the patient achieved PR according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (*Figure 3*).

However, because the patient was not tolerant to this regimen and vomited a lot during the treatment, we changed the therapy into a vascular endothelial-derived growth factor (VEGF) inhibitor, bevacizumab combined with FOLFOXIRI (fluorouracil, folic acid and irinotecan) for one cycle. Unfortunately, his CA19-9, CA125, total bilirubin (TBIL) and direct bilirubin (DBIL) increased rapidly within two weeks (*Tables 1*,*2*). Liver MRI also showed that some nodules were larger than previous. It seemed the conventional triplet chemotherapy regimen did not work on this patient.

It has been reported that *BRAF* V600E CRC patients treated with the spartalizumab (PDR001), dabrafenib plus trametinib were well-tolerated and had favorable and

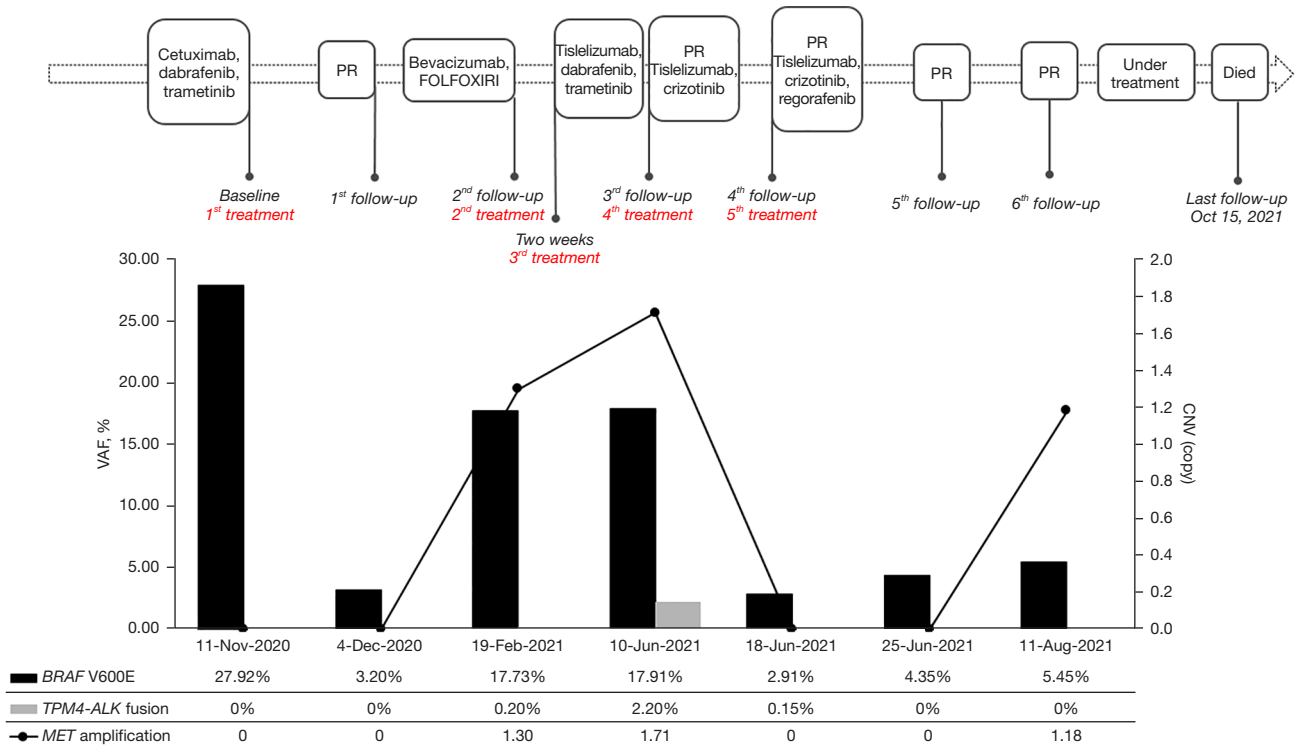

Figure 2 A timeline indicating patients received different treatment strategies. RECIST evaluation, and driver mutation of circulating tumor DNA. PR, partial response; VAF, variation allele frequency; CNV, copy number variation; *BRAF*, Raf murine sarcoma viral oncogene homolog B; *TPM4*, tropomyosin 4; *ALK*, anaplastic lymphoma kinase; *MET*, mesenchymal-to-epithelial transition factor; RECIST, Response Evaluation Criteria in Solid Tumors.

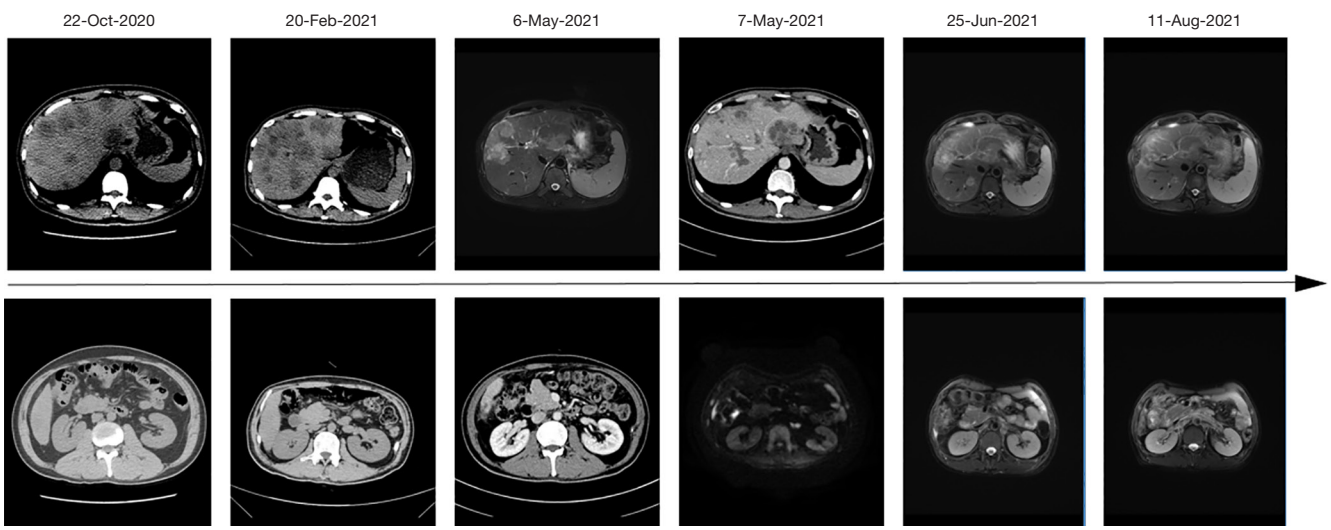

Figure 3 Computed tomography and the magnetic resonance imaging scans identified primary colorectal cancer and liver metastases after different treatment regimens.

Table 1 Measurements of serum tumor marker levels at different follow-up times

Biomarkers	Oct. 2020	Nov. 2020	Dec. 2020-1st	Dec. 2020-2nd	Jan. 2021-1st	Jan. 2021-2nd	Feb. 2021-1st	Feb. 2021-2nd	Feb. 2021-3rd	Mar. 2021	Apr. 2021	May 2021	Jun. 2021
CEA (ng/mL)	46.3	136.1	27.8	11.7	3.8	2.8	3.8	7.1	9.4	11.2	10.7	16.9	17
CA19-9 (U/mL)	12,000	12,000	12,000	10,902	3,946	10,816	12,000	>12,000	>12,000	>12,000	4,129	>12,000	3,546.1
CA125 (U/mL)	932.6	1,713	488	227	178	331	659	1,361	1,320	577	104	134	95.4

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125.

Table 2 Measurements of biochemical marker levels at different follow-up times

Biomarkers	Feb. 2021	Mar. 2021	Apr. 2021	May 2021
TBIL (μmol/L)	81.6	39.2	23.4	18.9
DBIL (μmol/L)	61.2	27.3	13.2	8.3
TBA (μmol/L)	78.7	3.4	2.9	5.2
GGT (U/L)	1521	914	507	425

TBIL, total bilirubin; DBIL, direct bilirubin; TBA, total bile acid; GGT, glutamyltranspeptidase.

durable response (18). After a thorough consultation within our medical team, communication with the patient and his family, the patient decided to receive this regimen. To avoid severe side effects, the patient was treated only with tislelizumab (200 mg, q3w) and trametinib (2 mg QD) first from March 1. The therapy was well-tolerated by this patient for 1 week, thus we added dabrafenib (150 mg, BID) for a better efficacy. During this period, TBIL decreased to 23.4 μmol/L and tumor biomarkers were generally stable (CEA and CA19-9 decreased and then increased, while CA125 continued to decrease) (*Table 1*). MRI and CT on May 6th showed that multiple metastases in the liver became smaller and some even disappeared, suggesting the treatment was effective (*Figure 3*). The regimen was then continued for about 3 months.

To further evaluate the efficacy, we performed NGS once again. Although the combined regimen of tislelizumab, trametinib and dabrafenib achieved good clinical efficacy, the *BRAF* V600E mutation frequency increased to 17.91%, accompanied by *MET* amplification (copy number ratio: 1.71) and *TPM4-ALK* fusion (frequency: 2.20%) (*Figure 2*).

Considering the presence of *MET* amplification and *TPM4-ALK* fusion, the patient finally agreed to change his regimen again and received a combination therapy of crizotinib (250 mg, QD) with tislelizumab (200 mg, Q3W) for 1 week. It was surprising that tumor biomarkers such as CA19-9 (from >12,000 to 3,546.1 U/mL) and CA125 (from 134 to 95.4 U/mL) decreased dramatically without any severe side effects (*Table 1*). One week later we added regorafenib (40 mg, QD). MRI scans on June 25 showed a PR in the primary tumor and liver metastases according to RECIST v1.1 (19) (*Figure 2*). NGS results showed *BRAF* V600E mutation frequency reduced to 4.35%, and previously co-occurring *MET* amplification and *TPM4-ALK* fusion were undetectable. This therapy has been continued up until now.

At the penultimate follow-up on August 11, abdominal MRI scan showed the local lesion and multiple liver metastases were slightly smaller. However, the wall of the flexura coli presented edema and became thicker than before. NGS analysis of peripheral blood showed a recurrence of the *MET* acquired resistant amplification mutation (*Figure 2*). It was assessed as PR (*Figure 2*). The patient is still under treatment of crizotinib, tislelizumab and regorafenib and within good physical condition. At the last follow-up on October 11, symptomatic treatment for obstructive jaundice continued to fail and the patient died on October 15, 2021. The patient finally achieved 11-month OS.

Discussion

Recently, with the emergence of liquid biopsy as a promising method for early diagnosis, therapeutic outcome assessment and prognosis prediction of tumor, plasmatic *BRAF* allele fraction (AF) has been demonstrated, and validated as an accurate prognostic factor in *BRAF* CRC treated with *BRAF* inhibitors (20,21). Circulating tumor DNA (ctDNA)-based dynamic monitoring has outstanding significance in reflecting the response of patients with advanced CRC. Currently, there are several studies on the prognostic value of ctDNA in CRC. Monitoring the change of ctDNA provided a comprehensive view of the patient's tumor burden, and therefore helps to guide clinical

decision-making throughout the disease course.

It is generally believed that *BRAF* mutations are mutually exclusive to *RAS* mutations, although co-existence has been reported in Beijing Hospital (22). The prevalence of *BRAF* mutations was recently reported to be as high as 21% in CRC patients in Norwegian registry (23) and 20.9% in Beijing Hospital (22). Patients with *BRAF* V600E mutation have been reported to have the worst prognosis among all *BRAF* mutations (7,24,25). Encouragingly, the development of novel targeted therapy has been proved to have fewer side effects and has a more promising efficacy (2). Previous studies have reported that dabrafenib plus trametinib was a new therapy with clinically meaningful anti-tumor activity and a manageable safety profile in patients with *BRAF* V600E NSCLC (26). Several studies have shown that *RNF43*-mutated represents a new biomarker for its potential to help prioritize anti-*EGFR/BRAF* combinations in mCRC *BRAF* V600E patients (27,28). However, this case is *RNF43* wild type in both tissue and plasma NGS analysis. The patient also adopted this regimen combined with a PD-1 inhibitor, tislelizumab. It did work on him and had acceptable short-time response.

During the treatment, we detected the *c-MET* amplification and *TPM4-ALK* fusion by NGS after triplet targeted therapy, which suggesting that the usage of their inhibitor would further improve the efficacy. Before this case, only one patient with *BRAF*-mutated and *MET* amplification had been reported, and this patient had benefited from conversion from anti-*EGFR* and -*BRAF* inhibition to a *MET* inhibitor plus *BRAF* inhibitor-induced tumor response (29). Since there was no safety or efficacy data, we just chose the low dose of crizotinib and regorafenib combined with tislelizumab. This therapy achieved a good clinical therapeutic effect without severe treatment-related side effects on this patient, thus providing a novel regimen design for CRC patients with *c-MET* amplification or *TPM4-ALK* fusion. This case uncovered liquid biopsy may help clinicians to tailor treatment and forecast patient prognosis, especial for tissue size may not be enough to conduct NGS. This case also demonstrated the importance of continuous monitoring of ctDNA during treatment, which could adjust or change the regimen based on the detection results for a better application of precision medicine.

Conclusions

In conclusion, we reported a rare case of a mCRC patient who presents co-existence of a *BRAF* V600E mutation, *c-MET* amplification and *TPM4-ALK* fusion. We continuously monitored the sequencing results of ctDNA, and changed the therapy regimen according to the results during the treatment, which showed that the novel combination of crizotinib, tislelizumab and regorafenib is a more effective and safer option for this type of patients. The frequency of driver gene mutations varied with the alteration of different regimen. Meanwhile, it would also result in whether the patient responded to the targeted therapy or progressed. The patient eventually achieved 11-month OS. Taken together, ctDNA monitor is indispensable during the treatment of mCRC patients and can be served as a promising tool during their follow-up.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-155/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-23-155/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-155/coif). Z.L. is an employee of Geneplus-Beijing (Beijing, China). 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 the 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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