

Combination nivolumab and bevacizumab for metastatic myxofibrosarcoma: A case report and review of the literature

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Abstract. The main therapeutic strategy for metastatic Myxofibrosarcoma (MFS) is palliative chemotherapy. A number of studies have demonstrated that anti-angiogenic therapy and immunotherapy could improve the survival rate of patients with metastases. However, the effectiveness of the combination of anti-angiogenic therapy and immunotherapy for the therapy of MFS is undetermined. The current study reports a case of metastatic myxofibrosarcoma that was treated with combination Nivolumab (monoclonal antibody, PD-1 inhibitor) and Bevacizumab (monoclonal antibody, anti-VEGF) after progression from the single use of Nivolumab. The aim of the current study is to assess the efficacy and safety of Nivolumab and Bevacizumab for metastatic myxofibrosarcoma and to review the literature. Up to the termination of the follow-up, the patient achieved a partial response for 16 months, had an overall survival for over 29 months since the metastasis and demonstrated a sustained benefit from treatment. The most frequent adverse events were fatigue, abnormality of Alanine aminotransferase (ALT), hypertension and proteinuria. Nivolumab and Bevacizumab treatment indicate beneficial clinical effects and are indicated to be safe to use in patients with metastatic myxofibrosarcoma.

Introduction

Myxofibrosarcoma (MFS) is a common type of soft tissue sarcoma that arises in the extremities of older patients. The principal therapeutic strategy for the tumor involves surgery with or without radiotherapy for localized disease, and palliative chemotherapy for metastatic disease (1,2).

It is currently estimated that ~60-70% of patients with MFS survive >5 years, while 35% of patients with high-grade

tumors are expected to develop distant metastasis. Numerous studies have demonstrated that both anti-angiogenic therapies and immunotherapies improved the survival rate of patients with metastatic sarcoma (3-5).

The present report presented a case of a 67-year-old man with recurrent metastatic MFS, who was prescribed a combination of the anti-angiogenic drug bevacizumab and the immunotherapy drug nivolumab. The patient achieved a partial response for >29 months and sustained benefit. This retrospective case study was approved by the institution review board of The People's Liberation Army No. 904 Hospital and the requirement for informed consent was waived.

Case report

The current case report presents a 67-year-old man diagnosed with localized MFS in the triceps brachii in the right upper arm (Fig. 1), who underwent surgical resection at the resection site in June 2015. The postoperative pathology revealed MFS of the right upper arm and the following major immunohistochemical markers: CD34(+), CD99(+), DES(-), NSE(-), SMA (-), S100 (-) and Ki-67 (10%+) (Fig. 2). However, a residual mass remained following the operation (Fig. 3). The first-line therapeutic strategy included surgical resection and radiotherapy, as chemotherapy was refused due to the frequently occurring side effects. On February 10 2017, the CT scan results revealed multiple lung metastases; the main lesion of the left lung was ~21.10x14.65 mm in size (Fig. 4). The gene status of the patient was analyzed using next-generation sequencing (NGS, whole genome sequencing, Illumina HiSeq) and the following results were obtained: i) A tumor mutational burden (TMB) of 6.7 mutations/MB; ii) the absence of microsatellite instability (MSI); and iii) negative PD-L1 expression (Panoramic gene test of Shihe 1; February 25 2017; internal sample number: b17021847377 Ge, p17021847378 Ge, f17021847379 Ge). As chemotherapy was refused, although the TMB was not high, nivolumab, a PD-1 inhibitor, was prescribed (3 mg/kg; every 14 days; Hong Kong Yanghe Hospital). The treatment lasted for 18 cycles between March and November 2017. On September 6 2017, the CT scan results revealed that the main lesion in the left lung was ~18.96x16.64 mm in size (Fig. 5), which suggested that the disease was in partial remission and the treatment was effective. On November 20 2017, the CT scan results indicated that the right lung metastasis site was locally

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enlarged (Fig. 6), and the main focus was ~29.14x26.01 mm in size, which according to the iRECICT standards indicated that the disease had progressed. Local radiotherapy (500 cGy; x7 times; Cancer Prevention and Treatment Center of Sun Yat Sen University) was subsequently used to remove the enlarged primary lesion. From December 28 2017, nivolumab (3 mg/kg; every 14 days; Hong Kong Yanghe Hospital; domestic purchase from August 28 2018) combined with bevacizumab (7.5 mg/kg; every 14 days) was prescribed. At the end of the follow-up period, the remission time of the combined treatment was 16 months, and the primary lesion was 14.86x11.1 mm in size, which was ~50% smaller compared with that achieved with either agent alone before the combination treatment. Notably, several of the foci had completely disappeared (Figs. 7 and 8). The total survival time was >29 months and a continuous benefit was obtained from the treatment. The predominant side effects of the treatment included fatigue, elevated ALT levels, hypertension and proteinuria (Fig. 9; Table I).

Discussion

MFS is one of the common types of soft tissue sarcoma, which occurs frequently in the extremities and subcutaneous tissues of the middle-aged and elderly population. The primary therapeutic strategies used to treat the disease include surgery, radiotherapy, chemotherapy and targeted therapy (1,2). For recurrent and metastatic MFS, the first-line chemotherapeutic strategy involves anthracycline and ifosfamide, and the second-line treatment includes gemcitabine and paclitaxel, of which the curative effect was discovered to be significantly reduced compared with the first-line treatment options (6). Trabectedin, an antineoplastic drug isolated from *Ecteinascidia turbinata*, a sea squirt of the Caribbean Sea, is currently the only second-line drug approved by the European Union for advanced soft tissue sarcoma following the failure of chemotherapy regimens based on anthracycline and ifosfamide (6). The median survival of the majority of the patients with advanced soft tissue sarcoma is usually <1 year, with only 10% of patients surviving >5 years (7).

Pazopanib is a second generation oral multitarget tyrosine kinase (TKI) inhibitor that targets VEGFR, FGFR and C-KIT, which is associated with the occurrence and development of multiple types of tumor. A phase II clinical study has previously demonstrated its efficacy in soft tissue sarcoma (8), while the subsequent phase III clinical study (PALETTE) indicated that pazopanib improved the disease progression free survival (PFS), but it was unable to improve the overall survival (OS) (9). In 2012, the US FDA approved the drug for the treatment of anthracycline-based non-fat soft tissue sarcoma, which represents the only oral drug approved by the US FDA for the treatment of advanced soft tissue sarcoma, except for liposarcoma (10,11). Anlotinib is a small molecular TKI compound with independent intellectual property rights manufactured in China, of which the targets are the same as Pazopanib. In 2016, ASCO reported the efficacy of the single agent anlotinib in advanced soft tissue sarcoma. In 2018, ASCO produced the results of its phase III study (ALTER0203); compared with the placebo group, the PFS of the anlotinib group was 4.8 months and the HR was 0.33. In addition, in the fibrosarcoma subgroup, the PFS of anlotinib

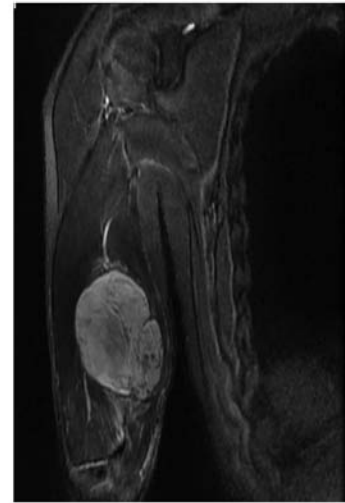


Figure 1. MRI scan revealed a malignant mass (size, 63x39x83 mm) in the triceps brachii muscle, located in the posterior part of the right upper arm.

group was 4.27 months, while the placebo group was only 1.43 months (12).

VEGF is an important inducer of angiogenesis, which has been revealed to promote the angiogenesis and proliferation of numerous types of tumor. Bevacizumab is a completely humanized anti-VEGF monoclonal antibody, which can specifically bind to VEGF, prevent the binding of VEGF and inactivate VEGFR-2, thus inhibiting the mitosis of endothelial cells and blocking the biological effects of VEGF (7). A retrospective study demonstrated that the sole treatment with bevacizumab inhibited metastatic or unresectable angiosarcoma and epithelioid hemangioendothelioma, of which 48% of the patients were stable and 15% were in partial remission (6). Another previous study investigating the combined treatment of bevacizumab and doxorubicin revealed that its effective rate was 12%, demonstrating a median OS of 16 months (5). In addition, in other soft tissue sarcomas, the combination of bevacizumab and chemotherapeutics, such as docetaxel, gemcitabine and temozolomide, also promoted several curative effects, which subsequently suggested a role for bevacizumab in the treatment of advanced soft tissue tumors (6).

Recently, accumulating research on PD-1 and PD-L1 inhibitors has demonstrated their efficacy in various types of malignant tumor, including soft tissue tumors (3,4). A phase II study (SARC028) also found that of those patients with recurrent and metastatic soft tissue sarcoma that received pembrolizumab, a PD-1 blocker, 1/40 patients achieved complete remission, 6 cases were in partial remission and 15 cases were in stable condition after 17.8 months of follow-up; these results suggested that PD-1 blockade immunotherapy for recurrent and metastatic soft tissue sarcomas may have an improved efficacy (4). Nivolumab is another PD-1 blocker, which has been the primary focus of several case reports and phase II clinical studies for the treatment of soft tissue sarcoma. It was previously hypothesized that nivolumab may serve a definite role in the treatment of soft tissue sarcoma (13-16).

The present case report presented a case of MFS. Following the diagnosis of lung metastasis, nivolumab was prescribed due to the patient refusing palliative chemotherapy, and the

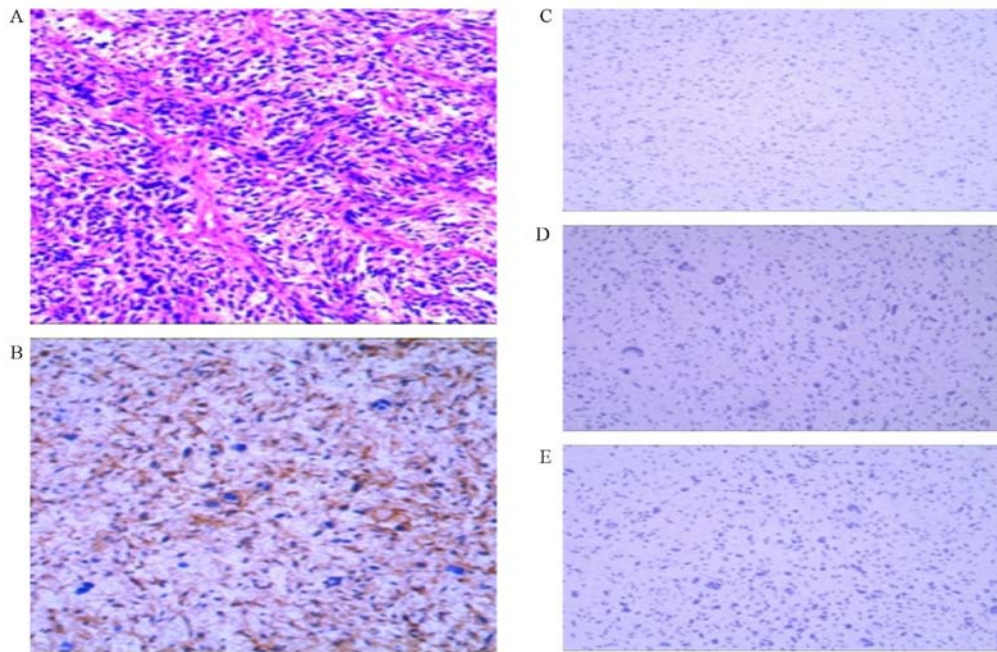


Figure 2. (A) Pathological diagnosis of myxofibrosarcoma (H&E staining; magnification, x200). The main immunohistochemical markers: (B) CD34(+), (C) CD99(+), (D) DES(+), (E) NSE(+), SMA (+), S100 (+) and Ki-67 (10%+).

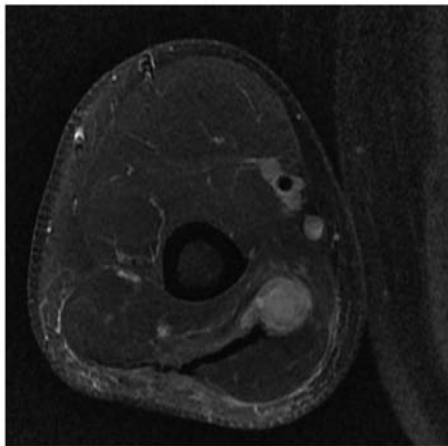


Figure 3. MRI scan from July 2015. The tumor remains on the margin of resection.

disease remained stable during the 18 cycles of treatment. After 8 months, several of the lung metastases sites were enlarged, indicating that the disease had advanced according to the iRECIST standards. Following local radiotherapy to remove the enlarged lesions, the combined treatment of nivolumab and bevacizumab was administered. The patient obtained continuous disease control and long-term survival benefits. Although several studies have concluded that radiotherapy combined with immunotherapy exerted an abscopal effect, the predominant principle of radiotherapy was considered to be its ability to promote an *in situ* tumor vaccine effect and reconstruct the immune microenvironment, amongst other functions. Generally, single high-dose radiotherapy and high-dose fractionated radiotherapy have been discovered to induce the abscopal effect; however, whether conventional radiotherapy may also induce the abscopal effect has not been

studied in detail, with the majority of the data stating that high-dose radiotherapy is the predominant means to induce the abscopal effect (17). It is suggested that radiotherapy itself may also promote immunosuppressive effects and affect the therapeutic effects (18). In addition, in a previous study, due to the exposure to external antigen environments, the immunogenicity of lung tissue was reported to be unique, and the number of infiltrating lymphocytes in the tumors was decreased compared with in the gastrointestinal and breast tumors, which was suggested to weaken the immune response induced by radiotherapy (18). More importantly, numerous studies have confirmed that the simultaneous combination of immunotherapy with radiotherapy for PD-1/PD-L1/CTLA-4 inhibitors was recommended to achieve the maximum effect, while immunotherapy followed by radiotherapy or radiotherapy followed by immunotherapy reduced the effect (19). However, in light of the results of the present case study, further investigations should focus on determining the efficacy of the combination with bevacizumab. For example, the combination of bevacizumab with PD-1/PD-L1/CTLA-4 inhibitors has previously demonstrated efficacy in clinical studies of other types of tumor, such as lung cancer. The principal mechanism of action of bevacizumab was discovered to be its ability to promote antitumor neovascularization, tumor vascularization and the improvement of the tumor microenvironment to render a 'hot tumor', which increased the local tumor lymphocyte infiltration and subsequently increased the efficacy of the PD-1/PD-L1/CTLA-4 inhibitors (20-23). In addition, a phase II study (APFAO; NCT03359018) revealed that the PD-1 inhibitor camrelizumab combined with the anti-angiogenic drug apatinib improved the PFS and OS of advanced osteosarcoma progressing following chemotherapy [https://clinicaltrials.gov/ct2/show/NCT03359018].

In the present case report, the NGS results revealed a TMB of 6.7 mutations/MB, the absence of MSI and negative PD-L1

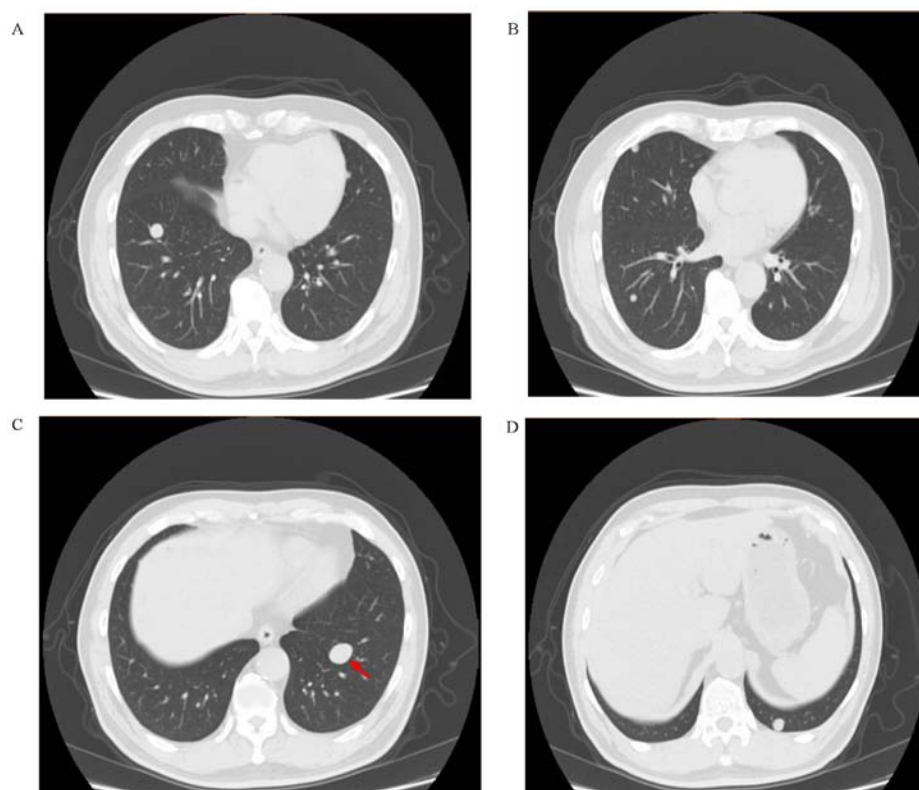


Figure 4. Chest CT scan from February 2017. (A-D) Multiple metastatic foci were present in the lung. Red arrow, the major focus (size, 21.10x14.65 mm).

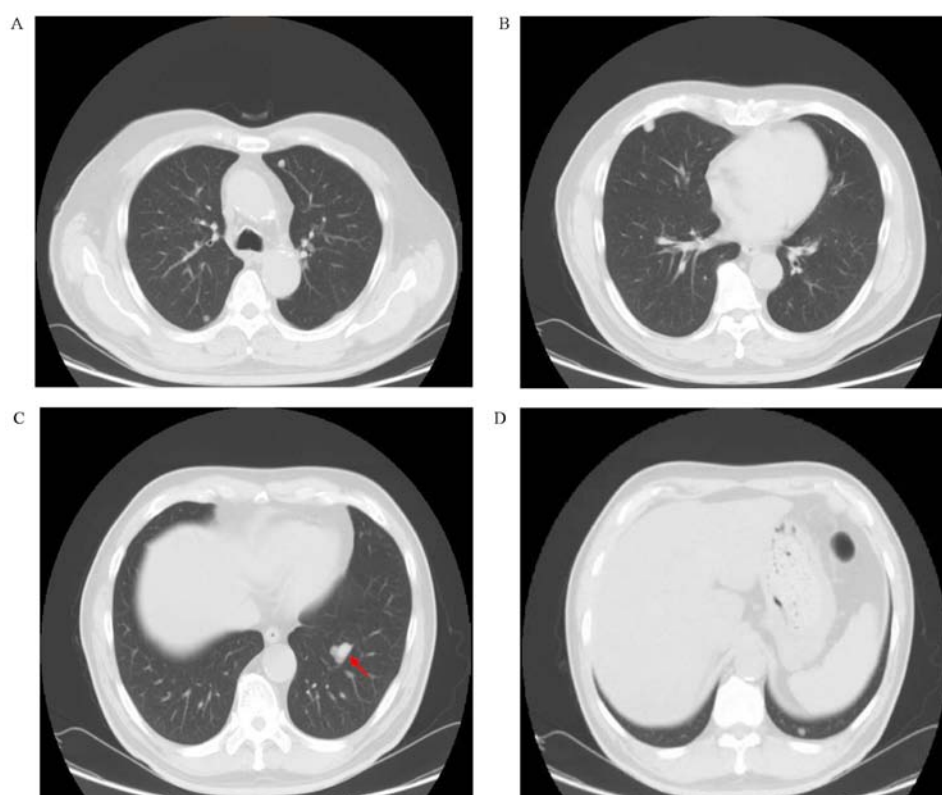


Figure 5. Chest CT scan from September 2017. (A-D) Multiple metastatic foci were reduced in the lung following nivolumab treatment. Disease P. Red arrow, the major focus (size, 18.96x16.64 mm). PR, partial response.

expression, which also verified that the above indicators may not be used as predictors of the efficacy of immunotherapy.

Thus, based on the improved efficacy of anlotinib following the failure of treatments such as nivolumab combined with

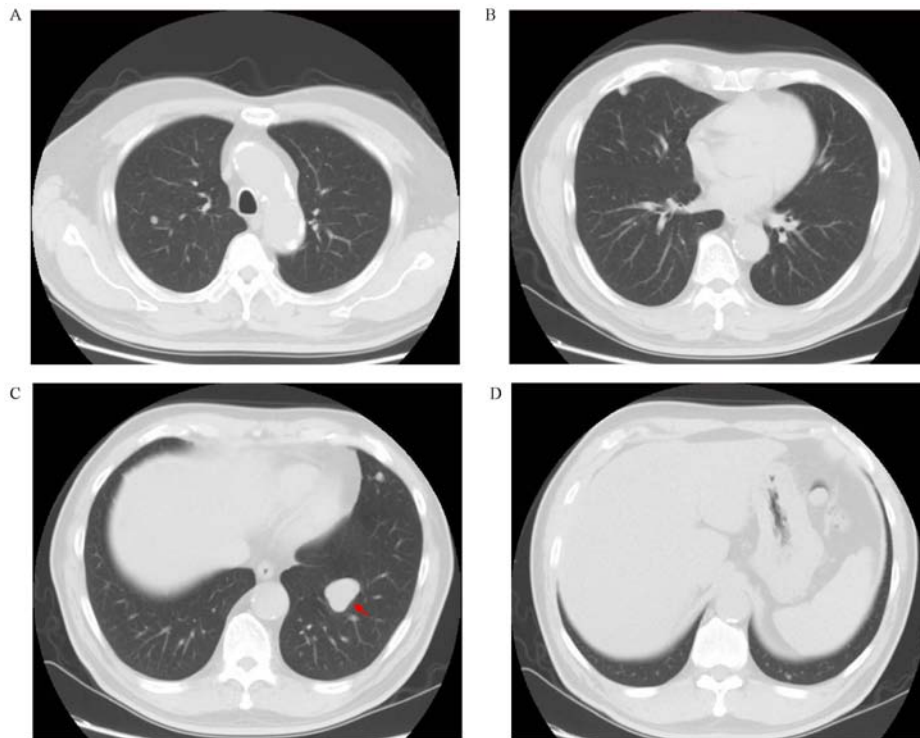


Figure 6. Chest CT scan from November 2017. (A-D) Several lung metastatic foci had diminished or disappeared, whilst some were enlarged. Disease PD. Red arrow, the major focus (size, 29.14x26.01 mm). PD, progressive disease.

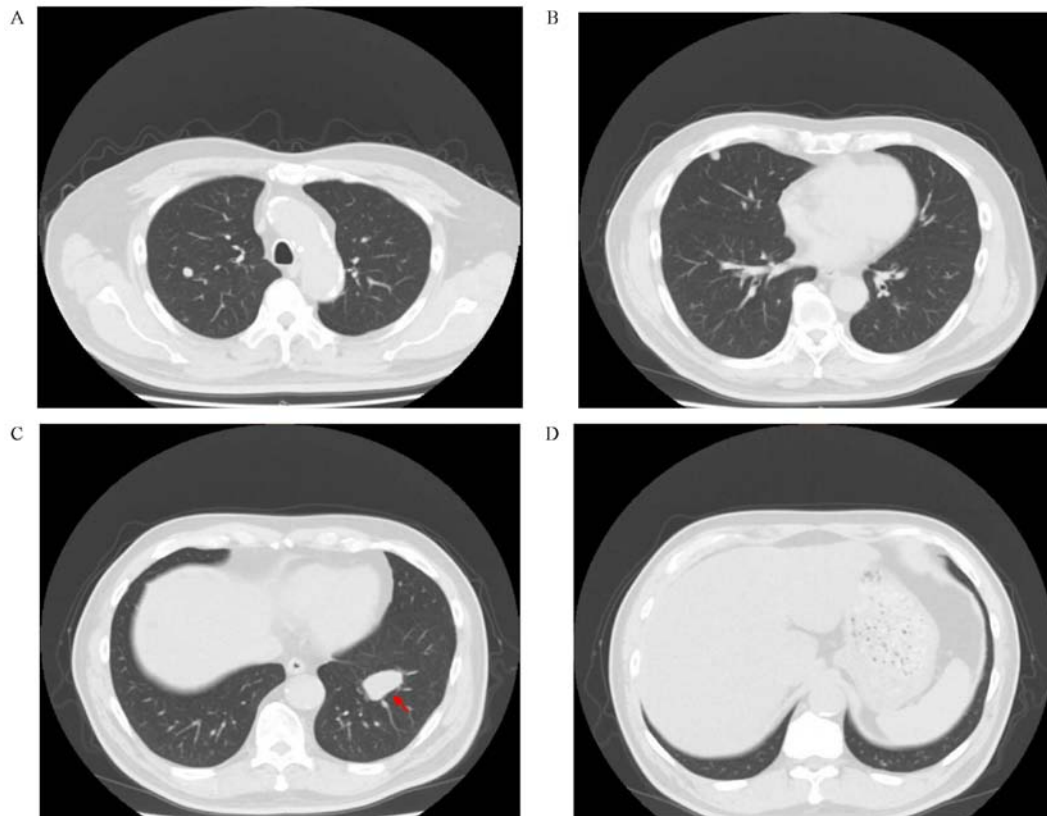


Figure 7. Chest CT scan from March 2018. (A-D) Several lung metastatic foci had stabilized or disappeared, demonstrating a sustained benefit from the combined treatment of nivolumab and bevacizumab. Disease SD. Red arrow, the major focus (size, 30.95x27.85 mm). SD, stable disease.

bevacizumab, anlotinib may be a good choice; however, further clinical research is required.

In conclusion, the treatment of the patient discussed in the current case study revealed the therapeutic effects

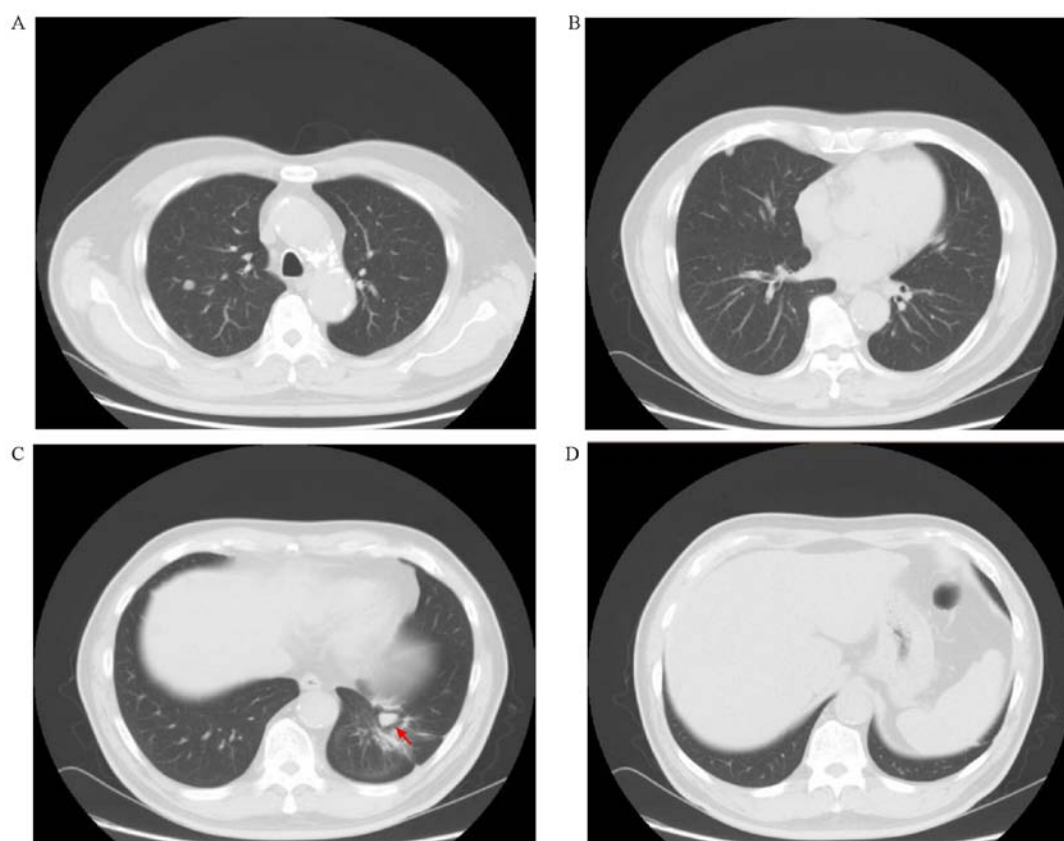


Figure 8. Chest CT scan from May 2019. (A-D) Several lung metastatic foci had diminished or disappeared, demonstrating a sustained benefit from the combined treatment of nivolumab and bevacizumab. Disease PR. Red arrow, the major focus (size, 14.86x11.17 mm). PR, partial response.

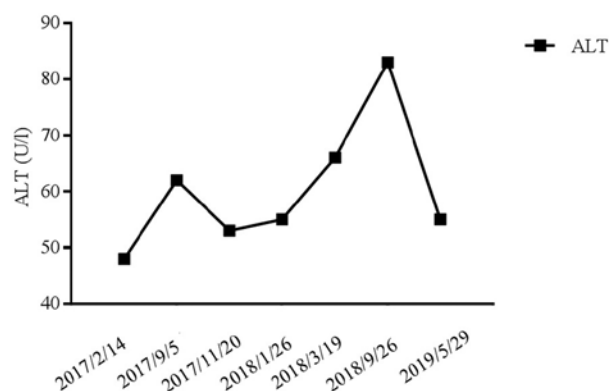


Figure 9. Alanine aminotransferase levels during treatment.

of nivolumab, a PD-1 blocker, in combination with bevacizumab; the patient obtained continuous remission and long-term survival benefits. The primary side effects included fatigue, abnormal ALT levels, hypertension and proteinuria, which were all safe and controllable. Thus, further phase III clinical studies are required to provide additional data to support the treatment of advanced MFS with a combination of nivolumab and bevacizumab.

Acknowledgements

Not applicable.

Table I. Management of adverse events during treatment.

Events	Grade	Measures
Fatigue	1	Observation
ALT	1	Diammonium glycyrrhizinate
Hypertension	2	Antihypertensive drugs
Proteinuria	1	Observation

ALT, alanine aminotransferase.

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Availability of data and materials

All data generated or analyzed during the current study are included in this published article or are available from the corresponding author upon reasonable request.

Authors' contributions

LS, DP and RZ were involved in conceiving and designing the study. LS drafted and wrote the manuscript. DP and RZ provided advice on the experimental design, interpreted the results and critically revised the manuscript.

All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The access of the database for the purpose of this study was approved by the Ethics Committee of The People's Liberation Army No. 904 Hospital (Jiangsu, China). As the hospital to which the patient was admitted is a teaching hospital, all patients admitted to our hospital signed a written consent in Chinese by which they agree that their medical data can be used in scientific studies.

Patient consent for publication

The participation in the study was approved by the patient and he gave his approval for the patient information presented herein to be published.

Competing interests

The authors declare that they have no competing interests.

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