Case Report

Major pathological response obtained after neoadjuvant chemotherapy combined with dual immunotherapy for malignant pleural mesothelioma: a case report

Yuchen Zhang[1#], Guangyin Zhao[1#], Chen Xu[2], Jie Gu[1*], Di Ge[1*]

[1]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai, China

Contributions: (I) Conception and design: D Ge; (II) Administrative support: J Gu; (III) Provision of study materials or patients: J Gu, C Xu; (IV) Collection and assembly of data: Y Zhang; (V) Data analysis and interpretation: G Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

[*]These authors contributed equally to this work.

Correspondence to: Di Ge, MD; Jie Gu, MD. Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Number 180, Fenglin Road, Shanghai 200032, China. Email: ge.di@zs-hospital.sh.cn; gu.jie3@zs-hospital.sh.cn.

Background: Malignant pleural mesothelioma (MPM) is a rare thoracic malignancy with high morbidity and mortality. A combination of systemic therapy and surgery may be a promising modality for the treatment of MPM, but evidence-based medicine is still lacking.

Case Description: Here we report a case of MPM. The patient presented to hospital with cough and sputum. After ineffective symptomatic treatment, computed tomography (CT) examination suggested a malignant tumor of pleural origin. Positron emission tomography/computed tomography (PET/CT) examination suggested no lymph node metastasis or distant metastasis. The pathologic diagnosis of MPM was confirmed after CT-guided puncture biopsy. Next, she underwent 3 courses of neoadjuvant chemotherapy combined with dual immunotherapy (carboplatin and pemetrexed combined with anti-CTLA4 and anti-PD-1), resulting in significant tumor shrinkage. After obtaining the patient's consent and completing a preoperative evaluation, we modified the extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) by performing a lower lobe resection and partial pleurectomy of the left lung. Intraoperative rapid frozen pathology suggested that the margins of the tumor were negative and complete resection was achieved. The postoperative pathology report showed 10% residual viable tumor, so the major pathological response (MPR) was achieved after treatment.

Conclusions: MPM might respond well to neoadjuvant chemotherapy and dual immunotherapy, improving the probability of complete surgical resection and attaining an encouraging pathologic response.

Keywords: Malignant pleural mesothelioma (MPM); neoadjuvant therapy; double immunotherapy; major pathological response (MPR); case report

Submitted Feb 28, 2024. Accepted for publication Apr 29, 2024. Published online Jun 21, 2024.
doi: 10.21037/tlcr-24-195
View this article at: https://dx.doi.org/10.21037/tlcr-24-195

Introduction

Malignant mesothelioma is a rare malignant tumor that originates from mesothelial cells and occurs mainly in the pleura and peritoneum, with malignant pleural mesothelioma (MPM or PM) being the most common. The five-year survival rate of MPM is only 5–10% (1). For systemic treatment of MPM, the National Comprehensive Cancer Network (NCCN) recommends pemetrexed in combination with platinum and bevacizumab as first-line treatment. However, the sensitivity to chemotherapy is not the same in different histological subtypes. The recently reported CONFIRM study showed a 3-month improvement in overall survival (OS) with nivolumab as compared with placebo. The checkmate-743 study demonstrated that double-immunotherapy with anti-PD-1 in combination with anti-CTLA4 was superior to chemotherapy alone (2), while it remains unknown whether chemotherapy combined with double immunotherapy can further improve patient prognosis. Based on the prolongation of OS brought by double immunotherapy and the benefits of surgical treatment for MPM (3), it is still a worthy attempt to cure MPM by surgical resection after neoadjuvant chemotherapy combined with immunotherapy. Here we report a case of MPM in a patient who underwent 3 courses of neoadjuvant chemotherapy combined with double immunotherapy (anti-CTLA4, anti-PD-1), resulting in significant tumor shrinkage and ultimately complete tumor resection by surgery, postoperative pathologic evaluation as major pathologic response (MPR). And we compared the changes in immune cells in the tumor microenvironment before and after treatment to investigate the microenvironmental changes caused by immunotherapy. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-195/rc).

Highlight box

Key findings

- Malignant pleural mesothelioma (MPM) might respond well to neoadjuvant chemotherapy and dual immunotherapy according to this single case.

What is known and what is new?

- MPM is a highly malignant thoracic tumor, and patients with locally advanced MPM have previously been treated with chemotherapy or dual immunotherapy (anti-PD-1 and anti-CTLA4).
- In this case, we found major pathologic response was obtained after neoadjuvant chemotherapy combined with dual immunotherapy for MPM.

What is the implication, and what should change now?

- Neoadjuvant chemotherapy combined with dual immunotherapy followed by surgical resection of the lesion may be a new approach to cure MPM.

Case presentation

A 69-year-old woman presented with cough and sputum one year ago and her condition improved after anti-inflammatory and symptomatic treatment for a lung infection. The patient reported improvement after two weeks of anti-inflammatory treatment and then stopped the medication on her own. Approximately six months after stopping the medication, the condition recurred and was more severe than the last time. At that time, her cough worsened and she developed sputum, and computed tomography (CT) scan revealed a mass located on pleural in the apical posterior segment of the left upper lobe and the dorsal segment of the lower lobe of the left lung, and she was considered to have a malignant tumor of pleural origin. Positron emission tomography/computed tomography (PET/CT) showed a solid mass seen in the left lung at the apical posterior end of the upper lobe and the dorsal end of the lower lobe, parietal to the pleura (at the level of 3^{rd}–6^{th} thoracic vertebrae), close to the adjoining pleura, with an abnormally elevated glucose metabolism. The maximum standard uptake value (SUV) was 14.8 and the mean CT value was 26.0 HU. There was no obvious increase in glucose metabolism in bilateral hilar, no obvious abnormality in hilar structure, size and density, and no obvious enlarged lymph nodes in hilar. There were no obvious enlarged lymph nodes in mediastinum. A CT-guided biopsy was performed (Figure S1), and the pathological result was an epithelioid cell-like malignant tumor, which was invasive growth. Immunohistochemistry showed TTF-1(–), NapsinA(–), calretinin(+), CK5/6(+), D2-40(+), WT-1(+), and STK11 gene mutation was detected, which led to the diagnosis of epithelial malignant mesothelioma.

After diagnosis, the patient received 3 courses of paclitaxel-carboplatin (PC) regimen chemotherapy [carboplatin 400 mg (300 mg/m^2) d1 + pemetrexed 720 mg (500 mg/m^2) d1, q3w] and combined with double immunotherapy (nivolumab 140 mg d1 + ipilimumab 50 mg d1, q6w). After the completion of the 3 courses of treatment, the tumor shrinkage was indicated by CT

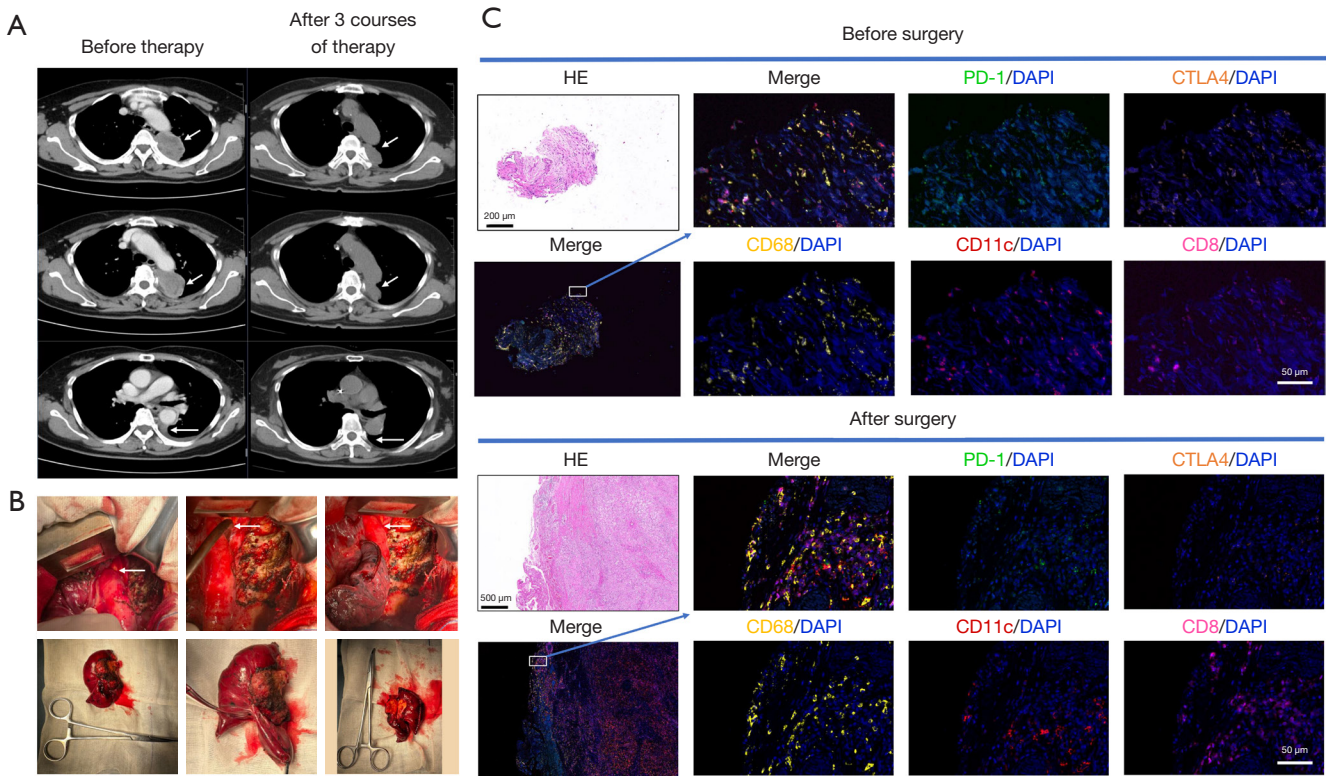

Figure 1 Imaging, pathology and intraoperative images of this case. (A) Computed tomography scans revealed the clinical response to combination therapy of chemotherapy and dual immunotherapy. Images before treatment are shown on the left and after three courses of neoadjuvant chemotherapy combined with immunotherapy on the right. Arrows point to lesions. (B) Anatomical location and relative size of lesions. Arrowheads indicate descending aortic origin. (C) Changes in immune-related indicators before and after treatment. Immunofluorescence was used to evaluate changes in PD-1/CTLA4/CD11c/CD68/CD8 in pre-treatment versus postoperative specimens. HE, Hematoxylin and Eosin.

scan (*Figure 1A*). Based on the measurements in the two CT images, the tumor was reduced from 79.6 mm × 49.9 mm × 35.5 mm to 40.0 mm × 38.5 mm × 16.4 mm after preoperative treatment.

Given the very significant shrinkage of the tumor, we decided to perform surgical treatment for the patient after thorough communication with her. One month after the end of treatment, surgery was performed. We modified the extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) by performing a lower lobe resection and partial pleurectomy of the left lung (*Figure 1B*). Intraoperative rapid frozen pathology (including the superior, inferior, medial, and lateral margins,) suggested that the margins of the tumor were negative and complete resection was achieved. Furthermore, immunostaining of the patient's lesions before and after treatment showed that the proportion of PD-1/CTLA4 T cells was significantly decreased, while the proportion of $CD8^+$ T cells was increased (*Figure 1C*). The preoperative proportion of $PD\text{-}1^+$ T cells and $CTLA4^+$ T cells accounted for about 40% and 20%, whereas the proportion of both decreased considerably postoperatively, with the proportion of $PD\text{-}1^+$ T cells at about 10% and $CTLA4^+$ T cells were barely visible in the field of view. In addition, the proportion of myeloid cells, especially $CD68^+$ macrophages and $CD11c^+$ dendritic cells, associated with immune effects was also significantly increased, which may be related to the patient's dual immunotherapy response in this case (*Figure 1C*).

X-rays were taken one month after surgery, and the images showed no fluid exudate in the chest, no air leak, and good lung reopening (Figure S2). The postoperative pathology report showed 10% residual viable tumor, so the major pathological response was achieved after treatment according to the criteria. The patient experienced only a

transient mild loss of appetite and no significant side effects throughout the treatment period. Currently, the patient has received the fourth chemotherapy combined with double immunotherapy after the surgery, and the double immunotherapy will be continued subsequently, and we will continue to follow up on this case. The timeline of this case is shown in Figure S3. 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.

Patient perspective

A little over a year ago, I went to the hospital with a recurring cough and phlegm. After taking oral anti-inflammatory medication my symptoms have lessened. But it did not last long. I started coughing again and again. This time I came to the hospital and the doctor suggested a CT scan for me. The results of the test shocked everyone which showed that there might be a malignant tumor present in the left side of my chest cavity and that it could be a highly malignant tumor originating from the pleura. At my doctor's recommendation, I had a PET/CT scan and a puncture biopsy. I was diagnosed with MPM through pathology. But thankfully, my tumor was localized and had not metastasized yet.

My team of doctors explained my condition in detail and treated me with my consent. The treatment plan was chemotherapy combined with dual immunotherapy, and none of us were sure if this would work for me. After completing each cycle of treatment, I had a review. Surprisingly, my tumors were shrinking. I have only felt an occasional loss of appetite during this treatment and no other uncomfortable symptoms. At the end of the three cycles of treatment, my doctor recommended that I undergo surgery to achieve complete removal of the tumor. After discussions between my family and me, we finally agreed to the doctors' treatment plan. Prior to the surgery, the doctors went over the surgical plan, which would remove a portion of my pleura and a portion of my lung.

My surgery went well. I recovered well after the surgery and had no discomfort other than dealing with the incision pain. My doctor told me that the pathology report showed the major pathological response was achieved after treatment.

Six months after the surgery, I was contacted by my doctor for written consent. A CT scan of the chest showed no signs of local recurrence. I am so grateful to the team of doctors who treated me for reclaiming my health.

Discussion

Surgical treatment of MPM remains controversial, including whether it is effective and which procedure to choose. The aim of surgical resection is to remove the tumor completely, but there are some arguments that it is difficult to achieve R0 resection with either the extrapleural pneumonectomy or pleurectomy/decortication surgical approach (4). Median/5-year survival was 20.7 months/17.9% in the intent-to-treat cohort and 23.2 months/21.2% in the macroscopic complete resection (MCR) group (3), demonstrating that macroscopic complete response remains one of the most important means that influences prognostic outcomes. Meanwhile, intraoperative use of hyperthermic chemotherapy has also been shown to be beneficial in improving the survival of MPM patients in several small clinical studies (5).

According to the NCCN guidelines, dual immunotherapy, i.e. nivolumab in combination with ipilimumab, is a first-line treatment for MPM. Checkmate743 study shows dual immunotherapy extends OS compared to chemotherapy in advanced MPM (2). In addition, chemotherapy combined with immunotherapy has been shown to improve median survival and response rates than chemotherapy alone in patients with advanced MPM (6).

For patients with advanced MPM, their survival can be prolonged with either chemotherapy alone or dual immunotherapy, but whether chemotherapy combined with dual immunotherapy is sufficiently safe and effective remains unknown. The ongoing DREAM3R Phase III trial will compare the clinical efficacy of Imfinzi in combination with standard chemotherapy versus chemotherapy alone in patients with MPM (7). In other solid tumors, neoadjuvant chemotherapy combined with immunotherapy achieved preoperative pathology downstaging. Given the significant survival benefits of surgical resection of tumors after neoadjuvant chemotherapy combined with immunotherapy in other solid tumors (8-10), surgery for advanced MPM patients after neoadjuvant chemotherapy combined with dual immunotherapy is also a very worthwhile treatment option to try.

In this case, the patient chose chemotherapy combined

with double-immunotherapy, and the lesion was significantly reduced after three courses of treatment. Inspired by checkmate817, keynote671 and other clinical studies, we decided to surgically remove the regressed tumor after fully communicating with the patient. Traditional pleurectomy requires complete removal of the pleura and is more damaging. In this case, only part of the pleura was involved, the lesion was mainly concentrated in the lower lobe of the left lung, and the tumor had shrunk significantly after preoperative treatment, so we modified the EPP and P/D by performing a lower lobe resection and partial pleurectomy of the left lung. We believe this was safe and effective for localized MPM. Such a procedure would cause minimal damage to the patient while ensuring complete resection of the tumor. In fact, the surgery also achieved R0 release, and the patient recovered well throughout the perioperative period. The achievement of MPR in this case indicates a potentially favorable prognosis, and we will continue to monitor this patient's condition in the follow-up.

Due to the relatively small number of surgical treatments and insufficient evidence from clinical studies, how to improve survival in patients with MPM remains an issue worthy of research, and this case report can bring some guidance to the future treatment of mesothelioma, especially neoadjuvant chemotherapy combined with double-immunotherapy. However, it is well known that the safety and efficacy of a therapy can never be assessed by a single case, and we are only giving one possibility in this case, which needs further guidance from multicenter clinical studies with large sample sizes in the future. It is worth our attention that there is a distinction between diffuse pleural mesothelioma and localized pleural mesothelioma in MPM, and it remains debatable whether this therapy is applicable to the different subtypes. We did not follow the RECIST criteria for this assessment because it requires a consistent method of CT scanning before and after treatment. Instead, the case was scanned with enhanced CT before treatment and with plain CT after treatment. We did not recommend the patient use PET/CT after treatment for economic reasons. This is a shortcoming of our case report and we will strictly follow the RESIST criteria in the future when evaluating the efficacy of similar patients.

Conclusions

MPM might respond well to neoadjuvant chemotherapy and dual immunotherapy according to this single case, improving the probability of complete surgical resection and attaining an encouraging pathologic remission.

Acknowledgments

Funding: This study was supported by the National Natural Science Foundation of China (82373371).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-195/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-195/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-195/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 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.

References

1. Milano MT, Zhang H. Malignant pleural mesothelioma: a population-based study of survival. J Thorac Oncol

2010;5:1841-8.
2. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-86.
3. Lapidot M, Gill RR, Mazzola E, et al. Pleurectomy Decortication in the Treatment of Malignant Pleural Mesothelioma: Encouraging Results and Novel Prognostic Implications Based on Experience in 355 Consecutive Patients. Ann Surg 2022;275:1212-20.
4. Janes SM, Alrifai D, Fennell DA. Perspectives on the Treatment of Malignant Pleural Mesothelioma. N Engl J Med 2021;385:1207-18.
5. Migliore M, Fiore M, Filippini T, et al. Comparison of video-assisted pleurectomy/decortication surgery plus hyperthermic intrathoracic chemotherapy with VATS talc pleurodesis for the treatment of malignant pleural mesothelioma: A pilot study. Heliyon 2023;9:e16685.
6. Piccirillo MC, Chu Q, Bradbury P, et al. Brief Report: Canadian Cancer Trials Group IND.227: A Phase 2 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma (NCT02784171). J Thorac Oncol 2023;18:813-9.
7. Smesseim I, Baas P. Immunotherapy Is a Good Standard Option for Patients With Malignant Pleural Mesothelioma, Despite the Real-World Results From Australia. J Thorac Oncol 2024;19:547-50.
8. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
9. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
10. Shang X, Zhao G, Liang F, et al. Safety and effectiveness of pembrolizumab combined with paclitaxel and cisplatin as neoadjuvant therapy followed by surgery for locally advanced resectable (stage III) esophageal squamous cell carcinoma: a study protocol for a prospective, single-arm, single-center, open-label, phase-II trial (Keystone-001). Ann Transl Med 2022;10:229.

Cite this article as: Zhang Y, Zhao G, Xu C, Gu J, Ge D. Major pathological response obtained after neoadjuvant chemotherapy combined with dual immunotherapy for malignant pleural mesothelioma: a case report. Transl Lung Cancer Res 2024;13(6):1420-1425. doi: 10.21037/tlcr-24-195