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Long-Term Disease Control With Second-Line Nivolumab Monotherapy in Malignant Pleural Mesothelioma: A Case Report

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Abstract

Nivolumab is recommended as second-line therapy for malignant pleural mesothelioma (MPM); however, durable responses remain uncommon. In addition, combination immune checkpoint inhibitors are frequently limited by immune-related adverse events. A 72-year-old man with epithelioid MPM underwent extrapleural pneumonectomy followed by adjuvant chemotherapy with cisplatin and pemetrexed. After recurrence, additional platinum-based chemotherapy was administered, followed by disease progression. Nivolumab monotherapy was then initiated as second-line therapy, resulting in a sustained radiological response. The patient has maintained progression-free survival for 24 months without severe immune-related adverse events, allowing long-term treatment continuation. This case highlights that nivolumab monotherapy may achieve durable disease control with a favorable safety profile in selected patients with MPM.

Categories: Cardiac/Thoracic/Vascular Surgery, Oncology, Pulmonology
Keywords: immune-related adverse events, malignant pleural mesothelioma, nivolumab, progression-free survival, second-line therapy

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive asbestos-related malignancy arising from the pleura and is associated with a poor prognosis despite recent therapeutic advances [1,2]. Recently, immune checkpoint inhibitors (ICIs) have expanded treatment options for MPM. Combination nivolumab plus ipilimumab has become an important first-line treatment strategy, while nivolumab monotherapy has emerged as an established second-line treatment option for relapsed MPM [1,2]. However, durable responses to nivolumab monotherapy remain uncommon in clinical practice, and their clinical characteristics have not been fully clarified.

In addition, combination ICIs are often associated with a higher incidence of immune-related adverse events (irAEs), including gastrointestinal, endocrine, and dermatologic toxicities, which may limit long-term treatment continuation [1,3-5]. In contrast, nivolumab monotherapy is generally better tolerated and may allow prolonged administration [2,6,7].

Here, we report a case of epithelioid MPM that achieved long-term progression-free survival (PFS) with second-line nivolumab monotherapy without severe adverse events.

Case Presentation

A 72-year-old man presented with low-grade fever and anterior chest pain. His occupational history included work in shipbuilding, ironworks, and construction, suggesting prior exposure to asbestos. Chest computed tomography (CT) revealed right pleural effusion and diffuse pleural thickening without lymphadenopathy (Figure *1A*, B). Positron emission tomography-computed tomography demonstrated increased uptake in the right pleura without evidence of distant metastasis (Figure *1C*, D). Thoracoscopic pleural biopsy confirmed epithelioid MPM.

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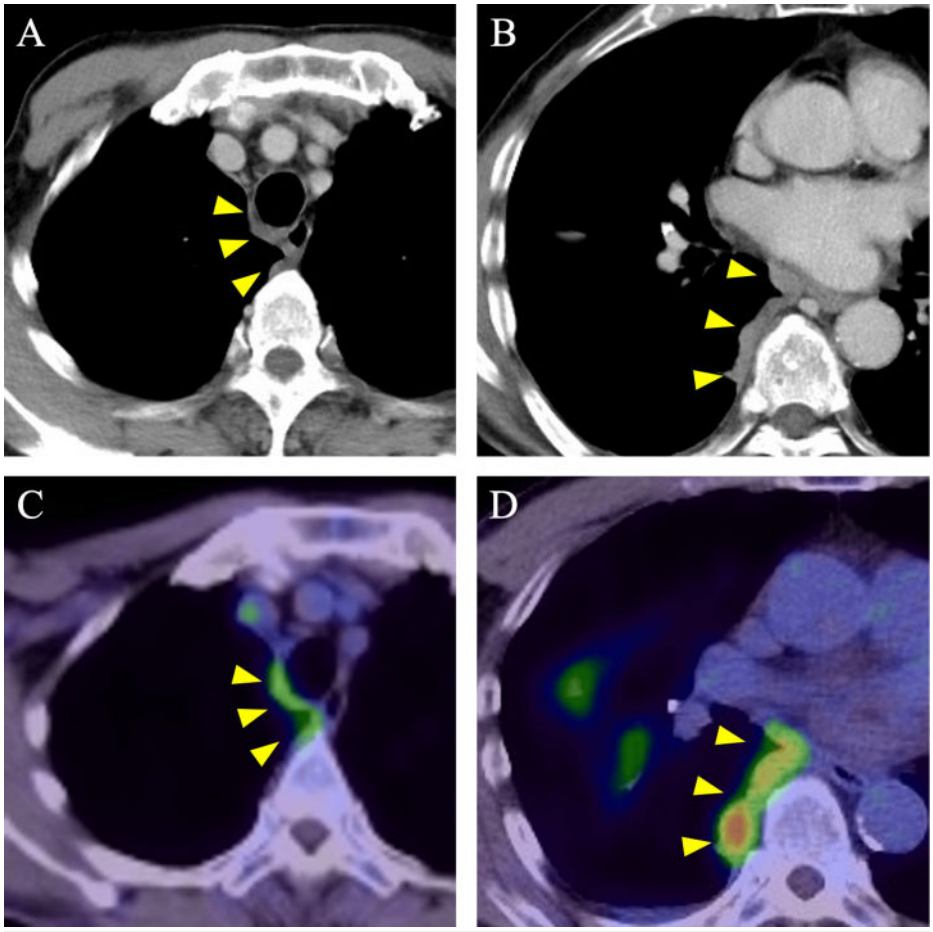

FIGURE 1: Chest computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) findings at diagnosis.

(A, B) Chest CT images showing diffuse right pleural thickening (arrowheads) associated with pleural effusion. (C, D) PET-CT images demonstrating increased fluorodeoxyglucose uptake in the thickened right pleura (arrowheads) without evidence of distant metastasis.

The patient underwent right extrapleural pneumonectomy with systematic lymph node dissection, including upper mediastinal lymph nodes (stations 2R and 4R), subcarinal lymph nodes (station 7), and right hilar lymph nodes (station 10R). No lymph node metastases were identified. Pathological staging was pT4N0M0 (stage IIIB). He subsequently received adjuvant chemotherapy with cisplatin and pemetrexed.

Recurrence with mediastinal lymphadenopathy was detected 31 months postoperatively, and six additional courses of cisplatin plus pemetrexed were administered, resulting in tumor shrinkage. Disease progression with regrowth of mediastinal lymph nodes and a newly developed chest wall lesion was observed 11 months after the initiation of first-line cisplatin plus pemetrexed chemotherapy (Figure *2A*, B).

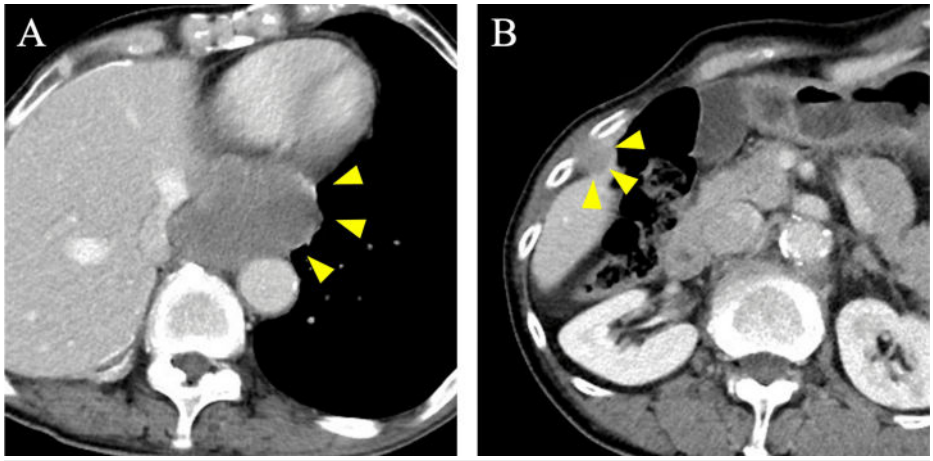

FIGURE 2: Chest computed tomography (CT) findings at disease progression before nivolumab initiation.

(A) Chest CT image showing enlargement of mediastinal lymph nodes (arrowheads). (B) Chest CT image demonstrating a newly developed chest wall lesion (arrowhead), consistent with disease progression.

Nivolumab monotherapy was initiated as second-line therapy at a dose of 240 mg every two weeks. The patient had an ECOG PS of 0 at the initiation of nivolumab. A radiological partial response with sustained near-complete resolution of both mediastinal lymph nodes and the chest wall lesion was observed (Figure *3*). The patient has received 47 cycles of nivolumab and has maintained PFS for 24 months without severe irAEs requiring treatment interruption or discontinuation (Figure *4*).

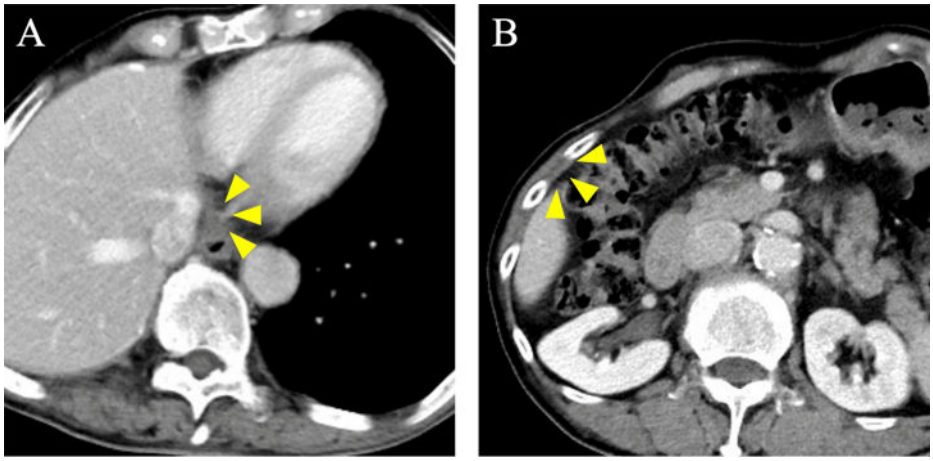

FIGURE 3: Chest computed tomography (CT) findings after nivolumab therapy.

(A) Chest CT image showing complete disappearance of the chest wall lesion at the previous lesion site (arrowheads). (B) Chest CT image demonstrating marked reduction of mediastinal lymphadenopathy, with near-complete resolution of previously enlarged lymph nodes (arrowheads).

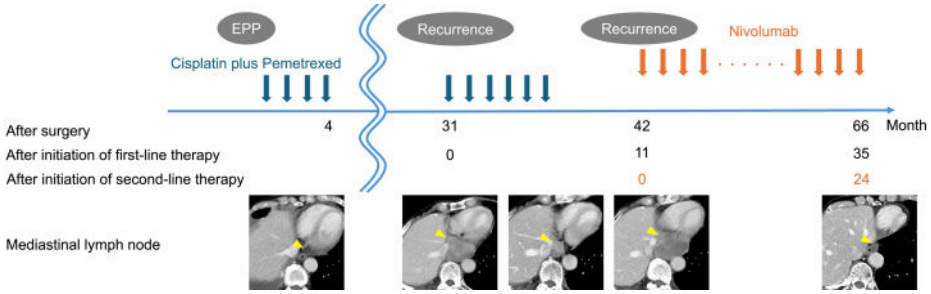

FIGURE 4: Overall clinical course and radiological response.

The timeline illustrates the patient's treatment course, including extrapleural pneumonectomy, platinum-based chemotherapy, and nivolumab monotherapy. Serial chest CT images demonstrate sustained near-complete resolution of mediastinal lymphadenopathy during the treatment course (arrowheads).

This figure was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, Washington).

Discussion

This case provides two important clinical insights. First, long-term PFS can be achieved with second-line nivolumab monotherapy in selected patients with MPM. Second, nivolumab monotherapy can be safely administered for prolonged periods without severe irAEs.

Regarding the first point, long-term PFS may be achieved with second-line nivolumab monotherapy in selected patients with MPM. MPM is associated with a poor prognosis despite recent therapeutic advances [1]. Although nivolumab is an established second-line treatment option, durable responses remain uncommon in clinical practice. In a randomized phase 3 trial, the median PFS for second-line nivolumab was reported to be approximately three months, indicating that prolonged responses are rare [2]. One possible explanation for the favorable outcome in this case is the relatively low tumor burden at the time of nivolumab initiation, following prior surgery and chemotherapy. Reduced tumor burden may enhance the efficacy of ICIs by facilitating immune-mediated tumor control [8]. However, tumor burden alone may not fully explain the variability in treatment response, and biomarker analyses may become increasingly important for identifying patients who could achieve durable benefit from ICIs. Nevertheless, predictive biomarkers for response to ICIs in MPM remain insufficiently established. Although tumor mutational burden (TMB) has been used as a predictive biomarker in several malignancies, its role in MPM remains unclear [9]. Similarly, the association between PD-L1 expression and the efficacy of ICIs in MPM has been inconsistent across studies; some reports did not demonstrate a clear association [2], whereas others suggested a trend toward greater benefit in PD-L1-positive tumors without definitive statistical significance [10].

Regarding the second point, this case suggests that nivolumab monotherapy may be administered safely over a prolonged period without severe irAEs. Nivolumab monotherapy is generally associated with a more favorable safety profile compared to combination ICIs. In the CheckMate 743 trial, grade 3-4 treatment-related adverse events occurred in approximately 30% of patients receiving nivolumab plus ipilimumab [1]. Previous studies have also reported higher rates of treatment discontinuation with combination therapy [3]. In addition, CTLA-4 inhibitors are associated with a higher incidence of severe irAEs compared to PD-1 inhibitors, including gastrointestinal, endocrine, and dermatologic toxicities [6,7]. Evidence from other malignancies also supports the increased toxicity of combination ICIs [4,5]. In this case, the absence of severe toxicity allowed long-term treatment continuation, which may have contributed to sustained disease control.

Taken together, this case suggests that second-line nivolumab monotherapy may provide both durable disease control and favorable tolerability in selected patients with MPM. Combination ICIs have become an increasingly important treatment strategy for MPM, particularly in the first-line setting. However, treatment-related toxicities may limit prolonged treatment continuation in some patients. Therefore, although the use of nivolumab monotherapy as second-line treatment may become less common in contemporary clinical practice, it may remain a valuable treatment option for selected patients in whom long-term disease control with acceptable safety is clinically important.

This report has several limitations. PD-L1 expression, TMB, and molecular profiling were not available. In addition, standardized response evaluation was not fully performed. Therefore, the biological mechanisms underlying this exceptional response remain unclear.

Conclusions

Second-line nivolumab monotherapy may achieve durable disease control with a favorable safety profile in selected patients with MPM. In the present case, long-term progression-free survival with sustained near-complete radiological response was achieved without severe irAEs, allowing prolonged treatment continuation. Although combination ICIs have become an important treatment strategy for MPM, nivolumab monotherapy may remain a valuable option for patients in whom long-term tolerability is clinically important. Further studies are warranted to clarify the clinical characteristics associated with durable response to nivolumab monotherapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shohei Otsuka, Kei Hiraoka, Nozomu Iwashiro

Acquisition, analysis, or interpretation of data: Shohei Otsuka

Drafting of the manuscript: Shohei Otsuka, Kei Hiraoka, Nozomu Iwashiro

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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