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Remarkable response to nivolumab in sarcomatoid malignant pleural mesothelioma with high PD-L1

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Keywords
Malignant pleural mesothelioma, nivolumab, PD-L1, sarcomatoid.

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Abstract

We report herein a case of sarcomatoid malignant pleural mesothelioma (MPM) with high PD-L1 expression who was refractory to standard chemotherapy but had a remarkable and sustained response to nivolumab. A 78-year-old man presented with right chest pain. Computed tomography (CT) showed a solid mass extending to the right pleura. Histopathological examination revealed the proliferation of spindle to pleomorphic ovoid shaped tumour cells, which are positive for calretinin and podoplanin. The patient was diagnosed with sarcomatoid MPM. Despite treatment with carboplatin and pemetrexed, the primary lesion rapidly progressed and new multiple pleural metastases were observed. Although his performance status decreased with advancing of symptoms and adverse events, nivolumab was administered. After the nivolumab treatment, CT showed a significant reduction in pleural tumours with a marked improvement in symptoms. In the primary specimens, TPS of PD-L1 was 80%. The patient has continued this treatment with sustained and remarkable effectiveness with good quality of life (QOL).

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumour primarily caused by asbestos exposure. Although current guidelines do not differentiate the treatment recommendations of advanced stages between histological subtypes of MPM, the sarcomatoid histological subtype hardly responds to systemic chemotherapy, showing a poor prognosis [1]. Nivolumab, a class of chemotherapeutic agents known as immune checkpoint inhibitors (ICIs), has been recommended as a treatment option for patients with MPM after first line chemotherapy. The efficacy of the programmed death ligand 1 (PD-L1) expression status as a predictive biomarker of the response to nivolumab in MPM patients is still not entirely understood. Herein we describe a case of a patient with sarcomatoid MPM with high tumour proportion score (TPS) of PD-L1 who was refractory to standard chemotherapy but had a remarkable and sustained response to nivolumab.

Case Report

A 78-year-old male patient presented with right chest pain. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. Computed tomography (CT) showed a solid mass with slight enhancement extending to the right pleura (Fig. 1A). Histopathological examination of the pleural tumour obtained with CT-guided percutaneous needle biopsy revealed the proliferation of spindle to pleomorphic ovoid shaped tumour cells arranged in fascicles and haphazard pattern. Prominent necrosis was also observed. Immunohistochemically, the tumour cells were positive for calretinin and podoplanin (D2-40), while they were negative for thyroid transcription factor 1, napsin A, carcinoembryonic antigen, p40, p63, and CD34. The patient was diagnosed with sarcomatoid MPM (Fig. 2A–C) and started on systemic chemotherapy. He received carboplatin (area under the plasma concentration versus time curve: 5) and pemetrexed (500 mg/m^2) after pleurodesis. Despite the treatment with two cycles of chemotherapy,

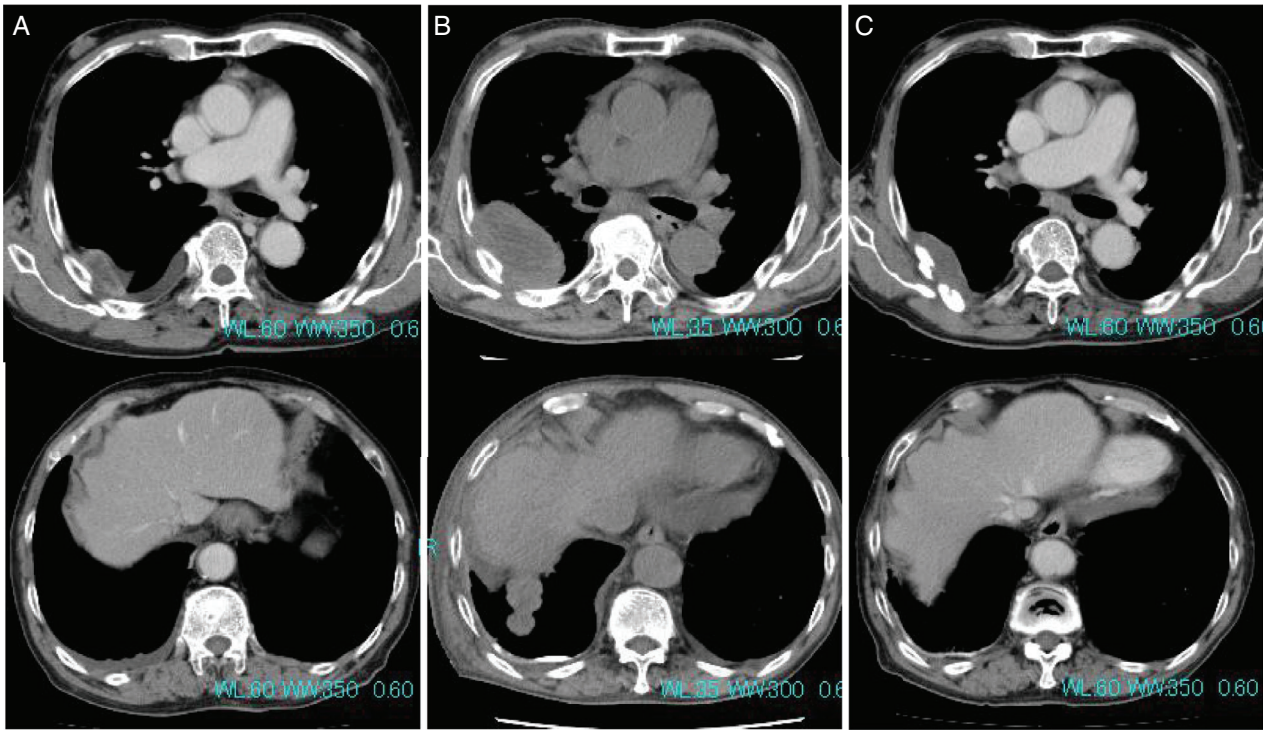

Figure 1. (A) Primary tumour on chest computed tomography (CT). (B) Chest CT after systemic chemotherapy showing an increase in primary tumour and new metastasizes. (C) Chest CT after immune checkpoint inhibitor revealing the remarkable tumour response.

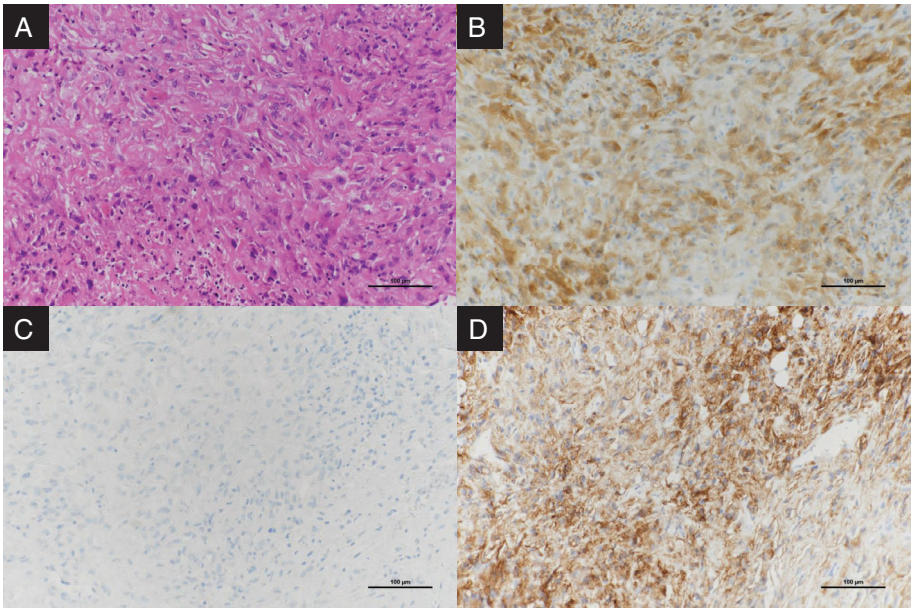

Figure 2. Sarcomatoid malignant pleural mesothelioma detected by percutaneous needle biopsy (Bar = 100 μm.). (A) Haematoxylin and eosin stain. (B) Calretinin. Immunohistochemistry. (C) Thyroid transcription factor (TTF) 1. Immunohistochemistry. (D) The programmed death ligand (PD-L) 1. Immunohistochemistry.

the primary lesion rapidly progressed and new multiple pleural metastases were observed (Fig. 1B). The patient's performance status decreased with increasing chest pain and adverse events caused by the chemotherapy. However, he was determined to try the next treatment, therefore, nivolumab (240 mg) was intravenously administered biweekly. After four cycles of nivolumab monotherapy, chest CT showed a significant reduction in pleural

tumours with marked improvement in symptoms. In the primary specimens, TPS of PD-L1 was 80% using the 22C3 assay (Fig. 2D). The patient has continued this treatment with a sustained and remarkable effectiveness and an improved quality of life one year after the initial diagnosis. (Fig. 1C).

Discussion

Malignant pleural mesothelioma is heterogeneous in its histological features. It is distinguished by three main histological subtypes, epithelioid, biphasic, and sarcomatoid mesothelioma. The epithelioid subtype is the most common form and has a high sensitivity and responsiveness to chemotherapy, which result in increased survival in comparison to the other subtypes of MPM. In contrast, sarcomatoid mesothelioma is a rare histologic type, which accounts for approximately 10% of all cases of mesothelioma [1]. A previous systematic review demonstrated that patients with sarcomatoid MPM receiving chemotherapy as the first-line treatment experienced a 13.9% response rate compared to a 21.9% response rate across all types of mesothelioma, suggesting resistance to chemotherapy in this subtype [1]. Sarcomatoid histological characteristics were also reported to be independent predictors of poor survival in MPM. Nivolumab, which is an anti-PD-1 monoclonal antibody, provides a survival benefit for patients with recurrent MPM with manageable toxicity, irrespective of the histological subtype and PD-L1 expression [2]. PD-L1 expression has been reported in 40% of MPM samples, with a higher rate in the sarcomatoid histotype, and has been associated with a poor prognosis [3]. A previous study has shown that some patients with sarcomatoid MPM, who responded to nivolumab show high TPS of PD-L1 (>50%), which is similar to the case described here [2]. Regarding the sarcomatoid type, several studies using ICIs for refractory MPM examined a small number of cases and found that the efficacy of PD-L 1 expression status as a predictive biomarker for the response to nivolumab may be limited [4]. Several chemotherapies may not have sufficient effects and may deteriorate the general condition in cases of sarcomatoid MPM. Although our patient showed a remarkable response to nivolumab with poor performance status, nivolumab is less effective in patients with a more advanced condition [5]. Patients with sarcomatoid MPM who undergo systemic chemotherapy may miss an opportunity to be treated with ICIs. This case suggests that ICIs would be expected to have a remarkable therapeutic effect on the patients with sarcomatoid MPM, and a high PD-L1 expression, and that the treatment strategies of advanced MPM may be distinguished between histological subtypes such as lung cancer.

Disclosure statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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