Trends in Immunotherapy 2024, 8(2), 8705.
https://doi.org/10.24294/ti8705

Case Report

A case of delayed initial response to combination ipilimumab and nivolumab in malignant pleural mesothelioma

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CITATION

Pillippu Hewa C, Khan Y. A case of delayed initial response to combination ipilimumab and nivolumab in malignant pleural mesothelioma. Trends in Immunotherapy. 2024; 8(2): 8705. https://doi.org/10.24294/ti8705

ARTICLE INFO

Received: 20 August 2024
Accepted: 12 September 2024
Available online: 26 November 2024

Abstract: Malignant pleural mesothelioma has a poor prognosis with limited therapeutic options Although numerous trials have shown that combination immunotherapy with nivolumab and ipilimumab is one of the first line treatments for patients with unresectable MPM, there is limited data on delayed responses over a long follow up period. We report a case of a delayed response 7 months after the cessation of immunotherapy in a patient who initially had progressive malignant pleural mesothelioma with metastases.

Keywords: malignant pleural mesothelioma; immune checkpoint inhibitor; ipilimumab; nivolumab; delayed response; immunotherapy rechallenge; overall survival

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy with a strong association to asbestos exposure where nivolumab and ipilimumab is the first line treatment of choice [1,2]. This has been shown to have much superior efficacy compared to platinum doublet chemotherapy [2,3]. Immunotherapies block inhibitory checkpoint receptors such as programmed death 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) to activate tumor specific immune responses leading to tumor cell destruction [4,5]. Although the DETERMINE Trial has shown no survival benefit of ipilimumab monotherapy over placebo, the most recent trials such as the MAPS2 trial and the CheckMate 743 trial have now shown that combining ipilimumab and nivolumab have resulted in a significantly higher overall survival rate over chemotherapy [4,6]. In this case report, we present a patient who experienced rapid disease progression with malignant pleural mesothelioma but had a delayed partial response to immune checkpoint inhibition with ipilimumab and nivolumab and further response on rechallenge.

1.1. Case report

In August 2021 an 81-year-old man presented to the Emergency Department with a 6 week history of worsening dyspnea. His past medical history was significant for hypothyroidism and a previous pituitary tumor which was resected in 2005. He was a non-smoker and had previous asbestos exposure while working in the Navy. A computed tomography scan of his chest showed a large right sided pleural effusion with some pleural thickening. A right sided thoracentesis was performed, and the pleural fluid showed proliferative species of mesothelioma, positive with calretinin

WT1, in keeping with pleural plaques and nodularity seen in the CT scan. His diagnosis was confirmed as malignant pleural mesothelioma. He then proceeded to undergo a staging CT abdomen and pelvis which showed a right pleural effusion and nodular noncalcified plaques in the anterior aspect of the right hemithorax in September 2021. He was subsequently enrolled in an AMPLE-3 study comparing Indwelling pleural catheterization (IPC) and TALC pleurodesis with VATs pleurodesis where he underwent IPC insertion and TALC pleurodesis. After a successful course of TALC pleurodesis, his IPC was removed, and further systemic treatment was discussed with the patient given his ECOG status of 1. However, it was the patient's preference to continue surveillance without commencing systemic treatment. Six months following his diagnosis, the patient deteriorated clinically with weight loss and worsening dyspnea. His repeat CT scan (**Figure 1**) showed increased pleural thickening by 5 mm and new pleural nodules. He was commenced on combination ipilimumab and nivolumab in February 2022 because of this progression. Unfortunately, his disease progressed rapidly three months into the commencement of immunotherapy. At this point, he had lost 25 kg. His CT scan in May 2022 showed significant disease progression and he was unable to perform his daily activities without experiencing shortness of breath. The decision was made to provide best supportive care and keep him comfortable due to clinical and radiological progression of the disease. However, 7 months after the cessation of his treatment, his follow up CT scan in December 2022 showed significant radiological improvement within the pleura itself. In addition to this, he had also improved clinically, with minimal shortness of breath and regained 25 kg of weight.

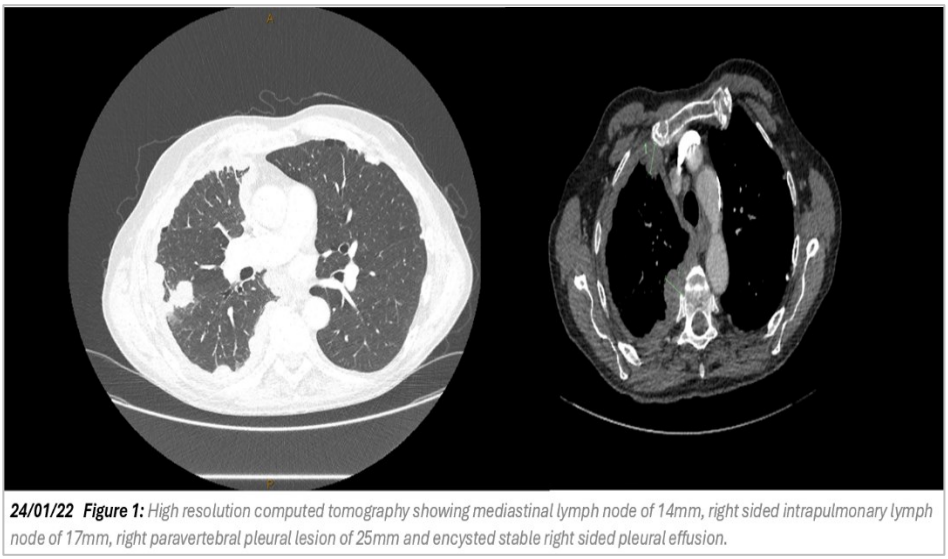


Figure 1. Follow up CT scan 6 months after diagnosis on surveillance only.

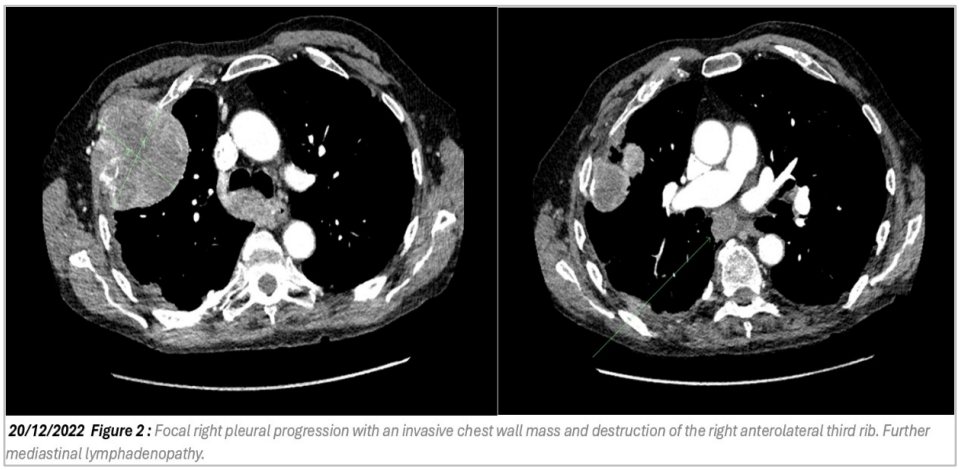
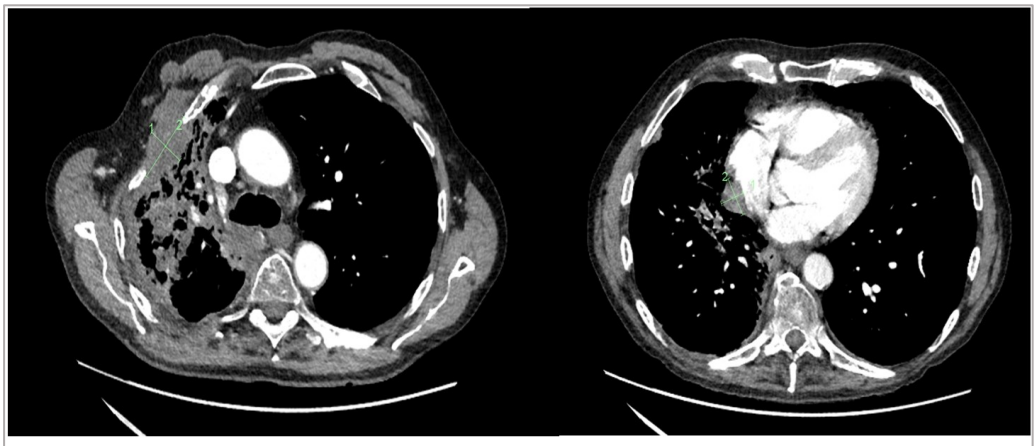


Figure 2. Repeat CT 1.5 years after diagnosis showing further progressin.

On subsequent scans (**Figure 2**), he was found to have an invasive right sided mediastinal mass extending to the right anterolateral third rib with mild intermittent chest pain. This led to the commencement of high dose palliative radiotherapy to the right chest wall and mediastinum for local control and symptomatic relief. He received 40.05 Gy in 15 fractions to the right chest wall and 30 Gy in 15 fractions to the mediastinum, which was well tolerated and improved his chest discomfort. A month following the completion of radiotherapy, he developed new onset right shoulder pain and tingling down the hand which coincided with a new soft tissue mass in the right upper lobe (RUL) causing nerve root compression in T1. His CT showed progression of the right hemithorax mesothelioma with further invasion into the intercostal space, progressive mediastinal upper abdominal retroperitoneal lymphadenopathy and a 56 mm sigmoid colon mass concerning for a metastatic deposit. He further underwent palliative radiotherapy (20–25 Gy) in 5 fractions to the RUL soft tissue mass and 8 fractions to the right lower lobe mass. After completing palliative radiotherapy (40 Gy to right chest wall and 30Gy to the mediastinum) in February 2023 and further palliative radiotherapy (25 Gy to the right upper lobe mass and 8 Gy to the right lower lobe mass) in April 2023, he was rechallenged with ipilimumab and nivolumab treatment in May 2023. His repeat CT chest on the 19th of July 2023 showed a significant interval decrease in the sigmoid colon mass, right anterior chest wall mass, right paramediastinal mass, subcarinal and paraeosophageal lymph nodes and right paravertebral pleural soft tissue masses (**Figure 3**). This CT chest further showed that the pleural thickening at the right atrium has improved from 29 mm to 10 mm and the pleural thickening at the right paravertebral region has improved to 13 mm from 14 mm. Similarly, the right chest wall mass anteriorly had improved from 45 × 26 mm from 49 × 30 mm while the sigmoid colon mass had improved to 26 × 27 mm from 32 mm previously. These findings coincide with at least a 50% reduction of disease volume at multiple sites radiologically. From a clinical perspective, the patient's shortness of breath had improved, and he had continued to tolerate immunotherapy without any significant toxicities. The follow up CT scan on the 31st of October 2023 demonstrated no evidence of mediastinal, axillary lymphadenopathy and fibrotic changes in the right hemithorax involving with calcified pleural thickening in the right lung, likely due to both his mesothelioma and the consequences of radiotherapy and

immunotherapy. On his most recent follow up in October 2023 he was commenced on steroid therapy due to the possibility of organizing pneumonia, but he reported to have significantly improved energy levels and exertional dyspnea. His serum albumin levels, and hemoglobin levels also returned to their baseline levels of 110 and 35 before his diagnosis, as shown by **Figure 4**.



19/7/23 Figure 3: *High resolution computed tomography showing significant interval decrease in the right anterior chest wall mass, right paramediastinal mass, subcarinal and paraoesophageal lymphadenopathy and right paravertebral pleural soft tissue masses. There is new consolidation of the lung suggestive of radiation pneumonitis.*

Figure 3. Follow up CT after radiotherapy showing a reduction in disease.

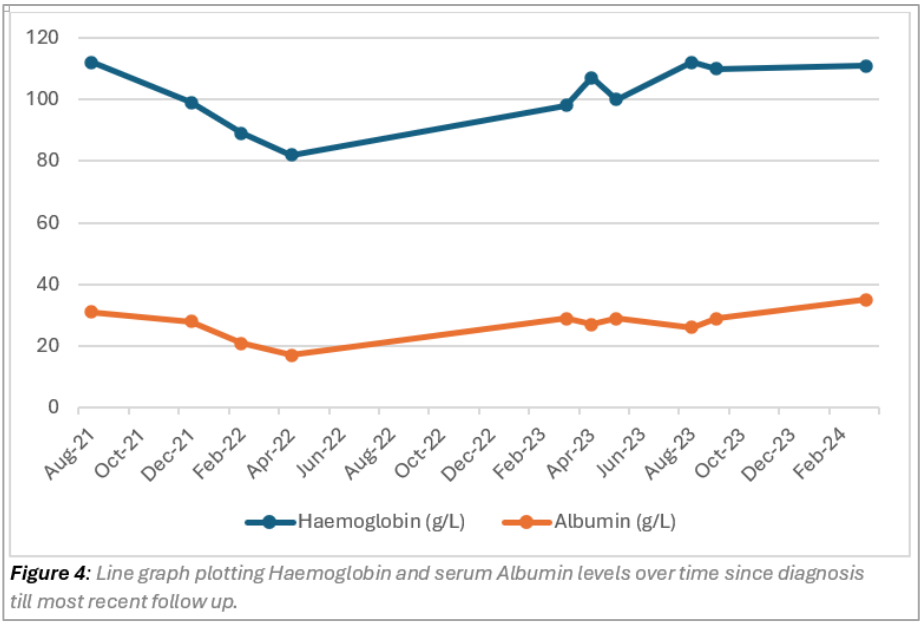


Figure 4: *Line graph plotting Haemoglobin and serum Albumin levels over time since diagnosis till most recent follow up.*

Figure 4. Plot of serum albumin and haemoglobin over time of follow up.

1.2. Discussion

We presented a unique case of an 81-year-old man with MPM who had an excellent delayed partial treatment response to ipilimumab and nivolumab immunotherapy as well as major partial response on rechallenge. Mesothelioma is known to have a dismal prognosis where the median survival is 4 to 13 months for untreated patients [7]. Treatment options remain limited as MPM is a rare and difficult disease to treat. The approach to treatment is based on the staging of the mesothelioma

and the resectability of the tumor, along with prognostic factors such as histological subtype, medical comorbidities and the ECOG status of the patient [8]. Unresectable malignant pleural mesothelioma has been conventionally managed with platinum and pemetrexed chemotherapy in the first line setting since 2004 [9]. While most of the evidence supporting the use of platinum and pemetrexed chemotherapy derived from phase II studies have indicated response rates usually less than 20%, the phase III study by Volgelzang et al. has shown a significantly improved response rate of 41.3% with the combination of cisplatin and pemetrexed chemotherapy in comparison to cisplatin alone in the treatment of MPM [10,11]. This study has also shown that cisplatin and pemetrexed chemotherapy provides a median overall survival of 12 months and a median progression free survival of 5.7 months [11].

However, over the recent years, immune checkpoint blockade has been proven to improve the survival outcomes of mesothelioma in the first line setting [12]. Ipilimumab is a cytotoxic T lymphocyte-associated protein-4 (CTLA-4) inhibitor which binds to the immunosuppressive CTLA-4 receptor expressed on CD4 + lymphocytes, antigen presenting cells and granulocytes proteins on lymphoid tissue preventing the activation of T lymphocytes against self-antigens [13]. Nivolumab is a PD-1 inhibitor which binds to PD-1 receptors inhibiting PD-1 ligands located on the surface of leukocytes directly inhibiting effector T cells to downregulate immune responses of cancer cells [13]. Nivolumab and ipilimumab were initially studied in a monotherapy second line setting in phase II and phase III trials [6]. The phase 3 CONFIRM trial demonstrated that nivolumab monotherapy led to a statistically significant improvement in progression free survival and overall survival in patients who had progressed with first line chemotherapy treatment for MPM [14]. Similarly, the MAPS2 trial and single-arm phase 2 INITIATE trial showed a significantly higher response rate to nivolumab therapy in patients who had MPM with a positive PD-L1 expression (> 1%) compared to those with PD-L1 negative tumor [15,16]. While these studies supported the use of ipilimumab and nivolumab in the treatment of unresectable MPM in a second line setting after progression with platinum-based chemotherapy, the FDA approval for the use of immunotherapy in a first line setting is based on the randomized phase III CheckMate 743 study [12]. In this study, 605 patients with MPM were randomized to receive nivolumab and ipilimumab for up to 2 years or chemotherapy with platinum and pemetrexed for a maximum of 6 cycles. The results showed that the 3-year overall survival rate of patients who received immunotherapy was 23% compared to a rate of 15% in patients who received chemotherapy [12]. Similarly, 28% of the responders had ongoing response in the immunotherapy arm versus 0% in the chemotherapy group at the three-year mark [12]. A subgroup analysis further revealed that improvements compared with chemotherapy were statistically significant among patients with a non-epithelioid histology and in those with PD-1 positivity [12]. The median duration of response was 11 months in the immunotherapy arm compared with 6.7 months in the chemotherapy arm [12].

In our case, the patient was adamant to continue surveillance after his diagnosis instead of proceeding with chemotherapy or immunotherapy. However, he was commenced on ipilimumab and nivolumab due to disease progression at the 6-month mark. Despite this, he developed worsening shortness of breath, and radiological progression of his mesothelioma. At this point, the decision was made to provide best

supportive care, however 7 months after his treatment he had significant clinical and radiological improvement.

Our patient's clinical response to immunotherapy was a delayed but exceptional response, with more than 50% of disease resolution both clinically and radiographically over a follow up period of 26 months. There is sparse literature available on a such a high delayed response rate as seen with our patient. A phase I trial has shown that nivolumab alone led to a partial response in 24% of patients at 12 weeks while 4 patients out of the 34 patients had stable disease for more than 6 months [13]. The INITIATE trial showed that 32% of patients with relapsed MPM had progressive disease at 12 weeks of treatment with ipilimumab and nivolumab and none had a complete response at this point [14]. Maria Disselhorst et al. also reported that 68% of patients had disease control, and two achieved a partial response after 18 weeks while one had a partial response after 24 weeks of treatment [14]. The median duration of response was as long as 14.3 months [14]. This can be compared with our patient who showed progression of disease after approximately 12 weeks of treatment but then proceeded to show a significant delayed response 10 months following the commencement of ipilimumab and nivolumab. Contrastingly, our patient received immunotherapy as well as radiotherapy which may have had a compounded effect. Intensity modulated radiotherapy for MPN is currently a research topic of interest in clinical trials and has been shown to significantly improve median survival in patients undergoing surgical/antiblastic therapy with very few cases of grade II-III toxicities [15,16]. While our patient did not have any surgical intervention, it is possible that the radiotherapy he received had also contributed to his exceptional response.

Although there are limited results on delayed and atypical responses with mesothelioma and immunotherapy treatment, several studies and case reports have shown atypical response patterns with immune checkpoint inhibitors [17–19]. These response patterns can be of a wide range including delayed response (DeR), hyperprogressive disease (HPD), pseudoprogressive disease (PsPD) and a dissociated response (DR) [17]. A systematic review revealed that a delayed response is most observed following initial stable disease and subsequent therapeutic responses [17]. Dissociated response patterns have also been found in patients receiving combination immunotherapy, particularly nivolumab with ipilimumab as well as PD-1/PDL-1 inhibitors with chemotherapy and/or radiotherapy [17,18]. Similarly, a case series investigating such patterns in patients with RCC receiving immune checkpoint inhibitors discovered that 10.9% of patients had a late response, while 8.7% had pseudo progression and 47.8% had a dissociated response [20]. The rate of dissociated response has also been found to vary between the type of solid cancer, of which mesothelioma had a 12.5% rate of showing a dissociated response [17]. Hence, while it is possible that our patient falls into the category of having a significantly delayed response with his immunotherapy, it is also possible that he initially displayed a dissociated response or even pseudo hyper progression after which followed a delayed partial response. However, a retrospective analysis has shown that pseudo hyper progression and dissociated responses are uncommon patterns, and their occurrence should only be considered taking into account the possibility of real progression and treating patients beyond progression [18]. In our case, it is more likely that this patient experienced a true progression, as his radiological findings of a new chest wall mass,

significantly larger pleural lymphadenopathy and even a sigmoid mass coincided with his clinical symptoms of further deterioration. Furthermore, as seen in **Figure 3** his hemoglobin and serum albumin levels continued to trend downwards when he had progression of disease from April 2021 to February 2022 and increased afterwards returning to his baseline prior to diagnosis in his most recent blood test in March 2024 when he had a significant clinical response. Therefore, he had initially showed extensive disease progression with a new mediastinal mass after the commencement of immunotherapy and was later found to have a delayed partial response both after the cessation of his first course of ipilimumab and nivolumab as well as on rechallenge.

1.3. Conclusion

The emergence of immunotherapy has been proven to provide more favorable outcomes in progression free survival, response as well as overall survival in patients with MPM. Here we report a case of a patient with MPM who experienced rapid disease progression 6 months after his diagnosis and had both a delayed exceptional radiological and clinical response after the commencement of ipilimumab and nivolumab immunotherapy as well as significant response on immunotherapy rechallenge. Our patient's case highlights the importance of monitoring closely over a longer follow up duration for a delayed immunotherapy response in MPM.

Ethical approval: Written informed consent was obtained from patient to publish this paper and the case report did not require further ethical approval.

Conflict of interest: The authors declare no conflicts of interest.

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