



## Case Report

# Pneumomediastinum Secondary to a Major Response to Nivolumab in Mesothelioma

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## Abstract

**Introduction:** Malignant pleural mesothelioma (MPM) is a rare entity associated with chronic asbestos exposure. Second-line immunotherapy (IT) treatment is associated with very limited benefit, although in selected patients, durable partial responses have been reported.

**Material and methods:** This case describes the evolution of a patient with MPM undergoing palliative pleurodesis at diagnosis who received second-line Nivolumab monotherapy at the Department of Medical Oncology of the Hospital Universitario Infanta Sofia and follow-up at the Department of Thoracic Surgery of the Hospital Universitario Puerta de Hierro.

**Results:** We describe the case of an 83-year-old patient diagnosed with MPM who, after palliative pleurodesis at diagnosis and 4 cycles of platinum-based chemotherapy, had an excellent response to Nivolumab monotherapy. As a consequence of this good response, he presented a pneumomediastinum and subcutaneous emphysema without pneumothorax when a mediastinal-pleural communication developed. Management was conservative and the patient, six months after discontinuation of treatment, is in response with complete resolution of this complication.

**Conclusion:** This case shows a dramatic response to second-line Nivolumab in advanced MPM with the development of a pneumomediastinum as a resultant complication. This finding has not been previously described in the literature.

**Keywords:** Malignant pleural mesothelioma; Anti-PD-1; Neumomediastinum

**Abbreviations:** MPM: Malignant Pleural Mesothelioma; IT: Immunotherapy; CPI: Checkpoint Inhibitors; EPP: Extrapleural Pneumonectomy; P/D: Pleurectomy/Decortication; anti-PD-1: Anti-Programmed-Death-1; VEGF: Vascular Endothelium Growth Factor; PD-L1: Programmed Death Ligand 1; OS: Overall Survival; TMB: Tumor Mutational Burden; PFS: Progression Free Survival

## Introduction

Malignant pleural mesothelioma (MPM) is a rare entity and its development has classically been associated with chronic exposure to asbestos [1]. Typically arises from the mesothelial surfaces of the pleural cavity but also arise from the peritoneal surface, the tunica vaginalis, or pericardium. MPM has a poor prognosis with a median survival between 6 and 18 months [2]. Symptoms usually present, similar to lung cancer, when the disease has spread intrathoracically and include mainly

dyspnea, cough and chest pain [3]. Radical surgical treatment options like extra pleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) combined with radiotherapy are very limited and have not shown benefit in randomized studies, so it is not considered standard treatment and is reserved for very selected patients. Palliative pleurodesis for the control of pleural effusion, sometimes large in these patients, is a very common practice in the management of MPM [4]. The combination of Cisplatin and Pemetrexed is considered the standard first-line treatment and is the mainstay of therapy for most patients with MPM. Several studies with checkpoint inhibitors (CPI) in the first- and second-line setting in MPM have shown very promising results, especially in aggressive subtypes such as sarcomatoid differentiation, with a significant increase in overall survival (OS) compared to standard chemotherapy [5,6].

We present the case of a patient with an excellent response to second-line administration of anti-PD-1 (anti-programmed-death-1) Nivolumab associated with the development of secondary pneumomediastinum, a complication not described to date in the literature.

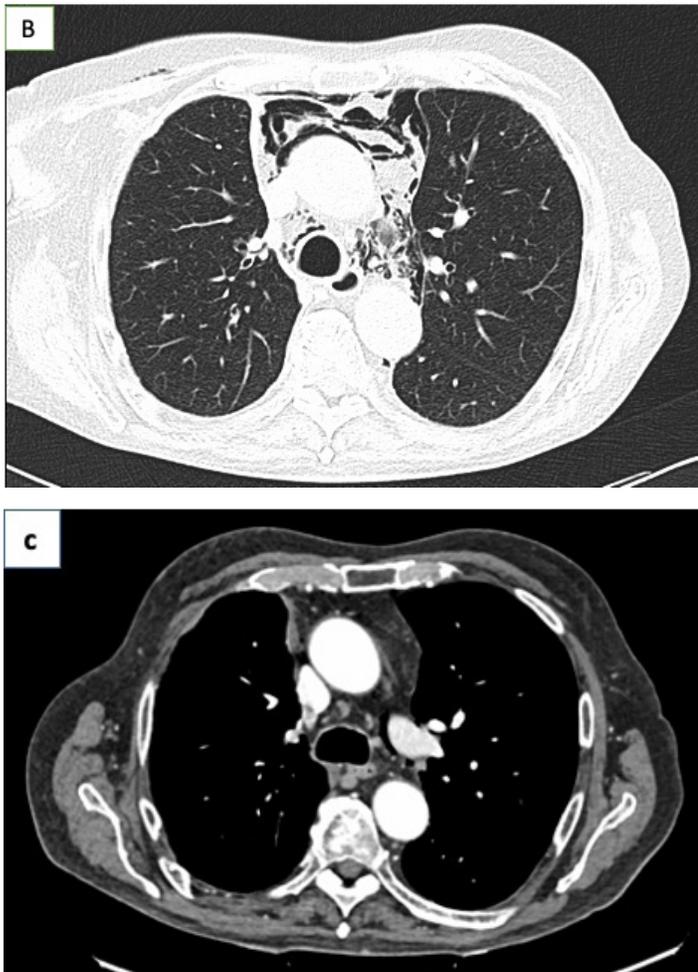
### Case report

83-year-old patient with history of hypertension and multinodular goiter was diagnosed by thoracoscopy of epithelioid mesothelioma T3N1M1 PD-L1 20%, no alterations in molecular sequencing with stable MMR phenotype (Figure A). A palliative pleurodesis was performed at diagnosis due to massive pleural effusion. He initiated Carboplatin (AUC 4)-Pemetrexed (500mg/m<sup>2</sup>) with stabilization as maximal response after four courses developing different complications: pneumonia, angina and febrile neutropenia, with a quick and complete recovery. Six months after starting chemotherapy, he had a pleural and pulmonary progression and initiated Nivolumab 240 mg biweekly with a rapid clinical benefit improving dyspnea and functionality. After the fourth cycle, he presented grade 4 immune-mediated hepatitis requiring hospitalization for a month and high doses of Metilprednisolona

(1,5 mg/kg/d) and Mofetil Micofenolate (2g/d), with a complete resolution. In a re-evaluation CT, after four courses with anti-PD-1, a greater radiological response of the pleural and pulmonary involvement, was evidenced. However, a pneumomediastinum was also observed, initially less evident, but it became more significant in the following days, adding subcutaneous emphysema without pneumothorax (Figure B a-b). The administration of oral contrast ruled out esophageal perforation. During the joint follow-up by Oncology and Thoracic Surgery, the patient remained asymptomatic, without dyspnea, cardiac disorders, fever or suspected signs of mediastinitis. Conservative management was performed with progressive radiological improvement. Currently, 5 months with treatment suspended, he has no evidence of progression of his oncologic process. As a consequence of the developed liver toxicity, Nivolumab administration was definitively discontinued. The patient is currently free of respiratory symptoms and the latest X-rays show a minimal residual pneumomediastinum.



**Figure A:** Multiple implants in parietal and mediastinal pleura corresponding to malignant pleural mesothelioma. Post-pleurodesis changes.



**Figure B and C:** Excellent response to Nivolumab in mediastinal and parietal pleura with development of pneumomediastinum and subcutaneous emphysema without evidence of pneumothorax in lung parenchyma window (B) and mediastinal window (C).

## Discussion

In this case report, we have presented an 83-year-old male patient who has shown a large and early clinical benefit after immunotherapy (IT) administered as a second-line treatment following the failure of chemotherapy. The exceptional aspect of this case and consequence of the excellent response of the implants, is that our patient has presented a pneumomediastinum and subcutaneous emphysema when necrosis of the implants occurred due to the action of the anti-PD-L1, generating a pleuro-mediastinal communication. The initial pleurodesis induced a decisive pleural fibrosis to avoid the generation of pneumothorax in this patient.

As previously mentioned, the standard first-line treatment for MPM, regardless of the histological variant, is the combination of platinum-pemetrexed. Several authors have demonstrated an increase in OS with the combination of this chemotherapy regimen with an anti-VEGF (vascular endothelium growth factor), Bevacizumab or Nintedanib [7,8]. Our patient did not receive anti-angiogenic drugs as this indication is not funded in our setting. He received 4 cycles with stabilization as the maximum response and with limited clinical benefit, as he developed various complications and toxicities, mainly analytical and cardiological, as previously described.

The irruption of the IT, specifically CPI in the treatment of solid tumors, and in this case, in MPM, has been a very interesting therapeutic alternative, especially in some subgroups, with promising results. We do not have predictors of response to IT, although some potential factors such as histological subtype, programmed death ligand 1 (PD-L1) expression, and tumor mutational burden (TMB) have been identified, although the results on their potential value as biomarkers are still uncertain [9]. Our patient had a PD-L1 expression of 20% and no microsatellite instability, which a priori did not make him a strong responder to IT, although as mentioned, we do not know with certainty what the most reliable predictors of response to this type of therapy are.

The Checkmate 743 study is a phase III study involving patients with advanced, multicenter MPM randomized to receive Platinum-based chemotherapy versus the combination of Nivolumab and Ipilimumab. With a follow-up of almost 30 months, median OS in the IT combination arm was superior to chemotherapy 18,1 months [95% CI 16,8-21,4] vs 14,1 months [12,4-16,2]; hazard ratio (HR) 0,74 [96,6% CI 0,60-0,91];  $p=0,0020$ ), with a greater benefit in those patients with non-epitheloid histologies: 18,1 months (12,2-22,8) vs 8-8 (7,4-10,2); HR 0,46 (95% CI 0,31-0,68 with similar G 3-4 toxicity rates in both arms [6]. Therefore, this combination could be established as the new standard in first-line therapy in the population with advanced MPM, although in our setting it is only approved for first-line use in patients with non-epitheloid histology. The data with anti-PD-L1 in second line are more discrete. The CONFIRM study is a phase III study that similarly included patients with platinum-pretreated MPM who were randomized to receive Nivolumab vs. placebo. This study demonstrated statistically significant benefit in OS and PFS in favor of Nivolumab, with acceptable toxicity in the experimental arm. However, in our setting, we do not yet have authorization to use this drug in the care setting, although it can be used on a compassionate use basis, as in the case of our patient [10]. The Keynote 028 study with a similar design with Pembrolizumab as experimental arm, although the standard arm was not placebo but chemotherapy (Gemcitabine or

Vinorelbine) showed no benefit of IT in terms of PFS (progression free survival) or OS [11]. Our patient had an excellent initial response to Nivolumab as mentioned above. Although tolerance to treatment was excellent, he presented different incidents, some of which led to the definitive discontinuation of the drug. Severe immune-mediated hepatitis occurs in about 5% of patients and usually resolves when treatment is stopped and steroids (1.5 mg/kg/d methylprednisolone) are added. In some cases, such as our patient, they become resistant to steroids and require a second step of immunosuppressants such as Mofetil Mycophenolate (2g/d), which was key to the onset of progressive improvement in liver parameters while maintaining coagulation intact at all times [12,13]. Given that with chemotherapy she had presented an acute ischemic heart disease event of the angor type, he was under supervision in the cardio-oncology department with serial troponin, ECG and pro-BNP controls with the intention of achieving an early detection of immune-mediated myocarditis [14,15] Finally, almost simultaneously with hepatitis, pneumomediastinum was incidentally detected in the initial re-evaluation CT scan, which showed a major partial response. After reviewing the literature, we have not found similar cases where, on the one hand, such a striking radiological response is described after a second line with Nivolumab in this context; and secondly, that this has been associated with the appearance of pneumomediastinum due to necrosis of the infiltrated pleura and the development of a self-limited mediastinal-pleural communication. Another cause of pneumomediastinum such as esophageal perforation, was ruled out after no leakage was observed with the administration of oral contrast. The management of this type of complication is conservative as long as there is no pneumothorax, as in this case, which would require thoracic drainage. In the short follow-up of the case (5 months) the patient remains responsive. It remains to be confirmed that the response obtained is maintained over time with longer follow-up and that this radiological response is associated with a benefit in PFS and quality of life.

## Conclusion

In this case report we present a patient diagnosed of advanced epitheloid MPM, pre-treated with platinum regimen with stabilization as maximal response, PD-L1 20% and MMR stable phenotype previously undergone to a palliative pleurodesis with a major response to Nivolumab after four courses with a neumomediastinum as exceptional complication. The patient remained asymptomatic at all times and was managed conservatively with regular clinical and radiological monitoring for 6 weeks with progressive improvement.

## Clinical Practice Points

- Second-line treatment with Nivolumab after platinum in patients with pleural malignant mesothelioma may be associated with significant clinical and radiological responses in selected patients.
- Necrosis of pleural implants induced by increased response to treatments (in our case, Nivolumab) could produce the development of pneumomediastinum in patients with previous pleurodesis.

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## Author's contributions

**MS:** Conception or design of the work; the acquisition, analysis, or interpretation of data for the work, drafting the work, final approval of the version to be published.

**DG:** Revising it critically for important intellectual content and final approval of the version to be published.

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