Case Report

Double immune checkpoint inhibitor therapy for unresectable pleural mesothelioma rarely induces hyperprogressive disease: a case report

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Background: Use of immune checkpoint inhibitors (ICIs) is associated with new response types, such as hyperprogressive disease (HPD), whose definition is still being discussed. Some authors use dynamic indexes to define HPD. However, since the Checkmate-743 study, ICIs have been a first-line therapy for pleural mesothelioma (PM), thereby making use of dynamic indexes less appropriate. The aim of this study is to describe two cases of HPD and then discuss its definitions and implications.

Case Description: Herein, we report two cases of PM HPD on first-line ICI therapy. A 67-year-old man with right unresectable epithelioid PM, without *BAP1* or *CDKN2A* losses, high neutrophil/lymphocyte ratio and rapid-onset pulmonary and mediastinal HPD after two ICI cycles, died of respiratory failure 1 month after starting treatment. A 40-year-old woman with left unresectable epithelioid PM had HPD at first assessment after 4 ICI infusions with jugular thrombosis, liver metastases and more dismal biological parameters. There are multiple different ways to describe HPD, some not applicable to PM. Suspected mechanisms include macrophage reprogramming to M2 cells. There are no known predictive factors of HPD, and future works should focus on identifying them.

Conclusions: HPD is a mode of progression for ICI-treated PM patients. Further investigation is needed to better define and anticipate HPD in these patients.

Keywords: Case report; pleural mesothelioma (PM); hyperprogressive disease (HPD); immune checkpoint inhibitors (ICIs)

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Introduction

Over the past decade, immune checkpoint inhibitors (ICIs) have greatly improved the prognoses of different cancers. ICIs have become the predominant option for first-line management of pleural mesothelioma (PM). The phase 3, open-label, Checkmate-743 trial (1), comparing first-line combination nivolumab + ipilimumab *vs.* standard chemotherapy (pemetrexed + carboplatin or cisplatin) for unresectable PM achieved, respectively, significantly prolonged median overall survival (OS), 18.1 *vs.* 14.1 months [hazard ratio (HR) 0.74], and 2-year OS rates, 41% *vs.* 27%.

Along with increased ICI use to manage cancers, new response types have been described, such as pseudo-progression, i.e., initial tumor size increases before it shrinks (2), or long-term response, which can result in an OS plateau. Hyperprogressive disease (HPD) is another response type recently associated with ICIs. It is defined as marked disease progression after starting ICI. However, no consensus HPD definition has yet been reached and it has rarely been described in PM. Because the Checkmate-743 study OS curves intersected early post-randomization, it is postulated that HPD could also concern ICI-treated PMs.

We report two patients treated with nivolumab + ipilimumab for unresectable PMs that underwent tumor progression early after starting ICIs and discuss the different HPD definitions, the potential pathophysiological mechanisms involved, and factors associated with HPD. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-382/rc).

Highlight box

Key findings

- Hyperprogressive disease (HPD) following immune checkpoint inhibitor (ICI) treatment exists in pleural mesothelioma (PM).

What is known and what is new?

- HPD is a new response type under ICI where patients undergo rapid tumor growth following treatment. It is associated with extremely poor prognosis. It has been described in other cancers.
- ICI is one of the new first-line treatment in PM. Data concerning HPD in PM are scarce. Its precise definition is still debated. Our cases suggest such responses exist in PM.

What is the implication, and what should change now?

- Given the poor prognosis of the rare HPD patients under ICI, more studies are needed to understand the mechanisms and risk factors of HPD to predetermine as best as possible which patients would benefit the best from each treatment.

Case presentation

Patient 1, a 67-year-old man, was diagnosed with right unresectable epithelioid PM with papillary contingent in June 2022. He was a non-smoker, had no professional exposure to asbestos, and no *BAP1* or *CDKN2A* losses. Genomic analyses found mutations in *TP53*, *NOTCH1*, *PDGFRA*, *MERTK* and *ATM* genes. His tumor mutational burden (TMB) was low (7.79 mut/MB). At diagnosis, his Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. Laboratory findings included: hemoglobin, 15.4 g/dL; total white cell count, 6.6 G/L; neutrophil/lymphocyte ratio, 6.5 (3); and albumin, 29 g/L. He received nivolumab + ipilimumab on July 8, 2022, and nivolumab alone on July 29, 2022. He was admitted in the emergency department 5 days later for Modified Medical Research Council (MMRC) grade-4 dyspnea which required 3 L/min of oxygen. Chest computed tomography (CT)-scan findings excluded pulmonary embolism and interstitial pneumonia, and revealed major PM progression (*Figure 1A*,*1B*) with mediastinal invasion. The patient died of respiratory failure 2 days later.

Patient 2, a 40-year-old woman, was a hairdresser and active smoker, with no comorbidities and no professional asbestos exposure. She was diagnosed on May 30, 2022, with left unresectable epithelioid PM, without *BAP1* or *CDKN2A* losses. Genomic and transcriptomic analyses found *TP53* and *NF1* mutations and *MET* overexpression. Her TMB was also low (10 mut/MB). At diagnosis, her ECOG PS was 1. Laboratory results included: hemoglobin, 12 g/dL; total white blood cell count, 17 G/L; neutrophil/lymphocyte ratio, 6.5; and albumin, 31 g/L. She received four ICI infusions—two cures of Nivolumab and Ipilimumab then Nivolumab alone—from June 14 to August 16, 2022. Her first-assessment CT scan showed major progression with jugular thrombosis (*Figure 1C*,*1D*) and hepatic metastases (*Figure 2A*,*2B*); and clinical and biological parameter deterioration (albumin, 24 g/L; hemoglobin, 8.7 g/dL) were observed. Thereafter, the patient received six carboplatin-pemetrexed cycles as second-line chemotherapy that achieved a partial response. Several months later, peritoneal carcinomatosis revealed tumor progression. Palliative care was decided, and the patient died 9 months after initial diagnosis.

All procedures performed in this study were in

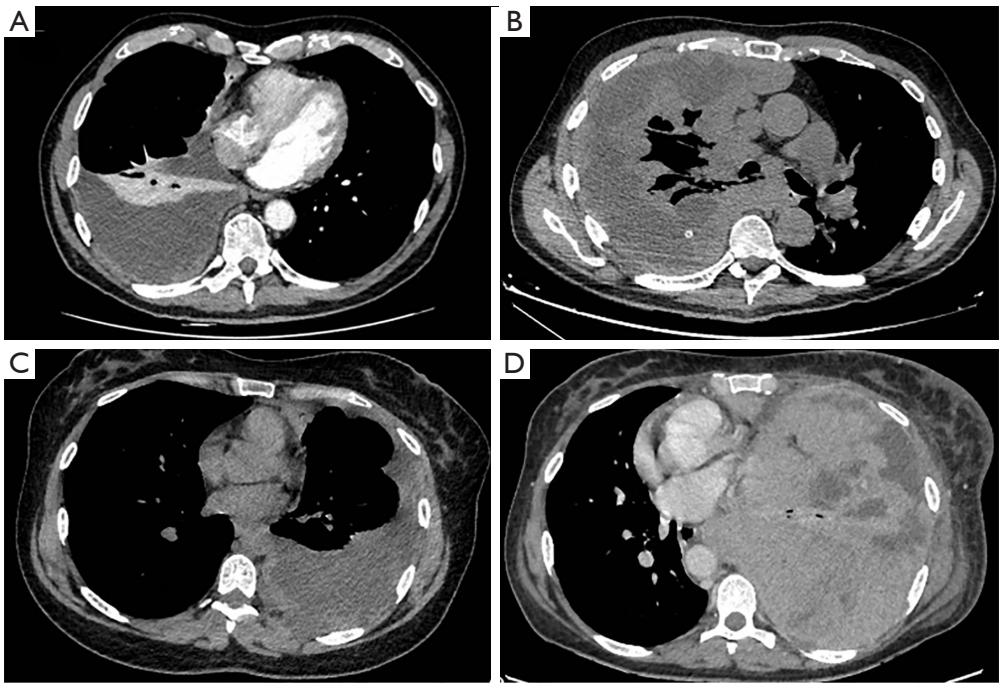

Figure 1 Key images from scans before and after ICI. (A) Scan from patient 1 before ICI. (B) Scan from patient 1 after ICI showing massive progression. (C) Baseline scan for patient 2. (D) Scan from patient 2 at first reevaluation. ICI, immune checkpoint inhibitor.

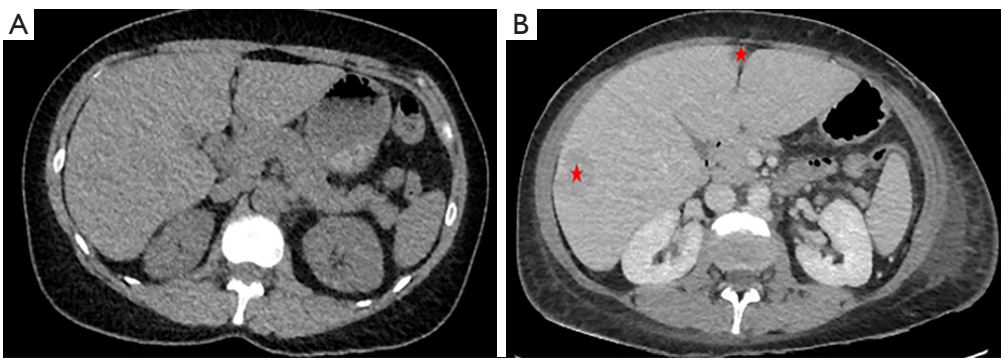

Figure 2 Key images of computed tomography scan showing liver metastases. (A) Abdominal scan from patient 2 at baseline. (B) Abdominal scan from patient 2 at first reevaluation showing liver metastases (highlighted by red stars).

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 for publication of this case report and accompanying images was not obtained from the patients or the relatives after all possible attempts were made.

Discussion

Several studies, on different cancer types, focused on the definition of HPD. Champiat *et al.* defined HPD as RECIST-defined progression and a two-fold increased tumor-growth rate (TGR) at first assessment following ICI administration (2). Using a 50% TGR threshold between first ICI dose and first assessment, Ferrara *et al.* (4) examined a retrospective cohort of ICI-treated non-small cell lung cancers (NSCLCs) and found 13.8% HPD. Other HPD definitions were also applied, specifically to NSCLCs. Lo Russo *et al.* used a multiparametric HPD definition meeting at least three of the following criteria (5): time-to-

treatment failure <2 months, >50% TGR increase, >2 new lesions in an already affected organ, dissemination to a new organ, clinical deterioration with PS becoming ≥2. That definition makes it possible to define HPD without two CT scans prior to treatment onset. It was strongly associated with a poorer outcome.

The two cases described herein would be classified as HPD according to Lo Russo *et al.*'s criteria. In a review focusing on HPD under ICI, Arasanz *et al.* (6) tried to identify the intrinsic characteristics of the patients developing HPD and their clinical risk factors. Multivariate analysis retained PS 1/2 (versus 0), female sex and age >70 years as being significantly associated with HPD (7). A meta-analysis of HPD in different cancers found liver metastases, metastases in more than two organs, serum lactate dehydrogenase increase or low programed cell-death protein ligand-1 (PD-L1) tumor expression to be associated with higher risk of HPD (8). Data on HPD in PM are scarce and there are no validated predictive markers of response or HPD in PM. The Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS2), defining HPD as a >50% TGR increase combined with RECIST-defined progressive disease (9), identified 6.4% of 223 patients. These numbers seem to match with our clinical impression that HPD in PM occurs rarely. Of note, 72% of these cases had negative PD-L1 expression. That is the only known report on PM HPD to date. Even though both our cases were epithelioid subtypes, there is no known association between HPD and histological subtypes.

The mechanisms involved in HPD remain unclear. It is hypothesized that ICI-triggered intra tumoral macrophage reprogramming into M2/CD163+ cells could be a cause for HPD, through a cross-talk between these myeloid cells and fibroblast providing proliferative and prosurvival signals (8). Moreover, high levels of interferon-γ, fibroblast growth factor-2 and β-catenin signaling could also be involved. A third hypothesis concerns the potential rewiring of onco-metabolic pathways (e.g., epidermal growth factor receptor) through an increase of regulatory T cells and their interactions with anti-PD-1 antibodies (8).

Even though HPD exists in PM under ICI, two real world studies published in 2024 found similar results to those in Checkmate-743, including older patients with worst average PS (10,11). We view this as a positive signal to keep treating a certain category of patients with ICI. The challenge is to determine which patients will benefit the best from this choice.

Conclusions

HPD, as in other ICI-treated cancers, is possible in PM patients managed with ICIs. Understanding the pathophysiological mechanisms and trying to highlight predictive risk factors based on the patients' or their tumors' characteristics remain a major challenge. It is now necessary to define PM HPD in a consensual manner in order to identify it correctly and subsequently develop predictive markers of response to ICI in order to assess which patient will benefit from such treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-382/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-382/coif). C.C. received grants, funding support, consulting fees and support for attending meetings from AZ, BI, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen. Jean-Bernard Auliac received grants, funding support, consulting fees and support for attending meetings from Boehringer Ingelheim, Hoffman-Roche, Takeda, BMS, MSD, Astra Zeneca, Amgen, Janssen and Pfizer. Jean-Baptiste Assie received funding support, consulting fees and support for attending meetings from BMS, GSK and Sanofi. The other 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 for publication of this case report and accompanying images was not obtained from the patients or the relatives after all possible attempts were made.

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