

# Hyperprogressive NSCLC With Two Immune-Checkpoint Inhibitors



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## ABSTRACT

**Introduction:** Immune-checkpoint inhibitors (ICIs) are transforming the modern era of cancer therapy. As new treatment options are becoming available, new patterns of disease behavior are manifesting. One such phenomenon, known as hyperprogressive disease (HPD), is a rare complication resulting in exponential disease progression on exposure to an ICI. Herein, we report an uncommon case of a patient who experienced HPD on 2 different occasions with 2 different immunotherapy agents.

**Case Presentation:** A 77-year-old black man was diagnosed with stage IV squamous cell carcinoma of the lung. He was enrolled in a clinical trial that involved viral transduction and stereotactic body radiation followed by pembrolizumab administration. His disease progressed markedly after the first cycle of immunotherapy. He was switched to carboplatin and protein-bound paclitaxel. He continued to have steady disease progression. After the third cycle of chemotherapy, he was again given immunotherapy, this time with atezolizumab. Again, after a single infusion, he exhibited substantial disease progression and further clinical deterioration.

**Conclusions:** HPD is a rare yet disturbing complication of immunotherapy with devastating effects on morbidity and mortality. Although there is accumulating literature supporting the phenomenon of HPD, to our knowledge, this is the first reported case of HPD occurring with 2 different ICIs in the same patient. This case suggests that the presence of HPD during treatment with 1 checkpoint inhibitor may preclude the use of another one. It also raises concerns about using other forms of immunomodulating agents. As immunotherapy becomes a major form of cancer therapy, more data are needed to better understand HPD and determine which patients are at risk.

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**Keywords:** Hyperprogressive disease; Non–small cell lung cancer; Stage IV; Pembrolizumab; Atezolizumab; Immunotherapy

## Introduction

Immune-checkpoint inhibitors (ICIs) have transformed the landscape of modern cancer therapy, particularly in advanced disease. Melanoma and NSCLC are 2 of the many malignancies in which patients have greatly benefited from this innovative therapy. The therapeutic response is measured by the Response Evaluation Criteria in Solid Tumors and includes complete response, partial response, stable disease, and disease progression.<sup>1</sup> Nevertheless, a small population of patients in clinical trials who received ICI had an unanticipated early crossing

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of progression-free survival and overall survival curves compared with those in standard chemotherapy.<sup>2</sup>

This phenomenon is associated with a rapid increase in tumor burden or growth and is now termed hyperprogressive disease (HPD). Although debate exists on whether patients truly experience accelerated growth versus ineffective therapy and typical disease progression, certain patients do experience tumor enlargement response that is consistent with hyperprogression. This case report describes the unusual scenario of a patient with metastatic NSCLC who developed HPD with 2 different ICIs on 2 different occasions.

## Case Presentation

A 77-year-old black man with history of chronic obstructive pulmonary disease (COPD) and 40-plus pack-years of smoking was admitted to the hospital with acute COPD exacerbation. Computed tomography (CT) of the chest revealed a 1.2-cm right lower lobe nodule and left-sided atelectasis. He was followed clinically, and 2 months later, a noncontrast CT revealed a necrotic mass in the superior segment of the left lower lobe measuring approximately 4 cm × 5 cm × 5 cm, along with a small left-sided, complex loculated effusion with pleural thickening (Fig. 1A and B). Subsequent bronchoscopy and biopsy revealed a fungating mass consistent with squamous cell carcinoma, and a bronchoalveolar lavage cytology specimen was positive for malignancy. Programmed cell death-ligand 1 (PD-L1) expression was present in 1% to 5% of the cells. Staging workup with positron emission tomography (PET) with CT revealed a similar-sized mass with increased uptake in the left lower lobe, an additional uptake in the left pleura, left pleural effusion, and a 2.7 cm nodule in the right adrenal gland, consistent with stage IV squamous cell carcinoma.

He was enrolled in a clinical trial consisting of an oncolytic viral transduction plus stereotactic body radiation therapy followed by pembrolizumab. He received his viral transduction a month later and was followed by 5 fractions of stereotactic body radiation therapy. Two weeks later, he received his first infusion of pembrolizumab. This was complicated by a hospitalization 3 weeks later owing to pneumonia. A repeat CT scan revealed interval hyperprogression of the cancer with the mass now measuring 10.7 cm × 10.8 cm, along with the development of several subcentimeter right lower lobe pulmonary nodules and an increase in the right adrenal mass to 3.9 cm (Fig. 1C and D). Given this rapid progression and clinical deterioration, he was taken off the trial and transitioned to systemic chemotherapy with carboplatin and protein-bound paclitaxel.

He tolerated the chemotherapy well, and after 2 cycles, he had another PET with CT scan. Although reduction in

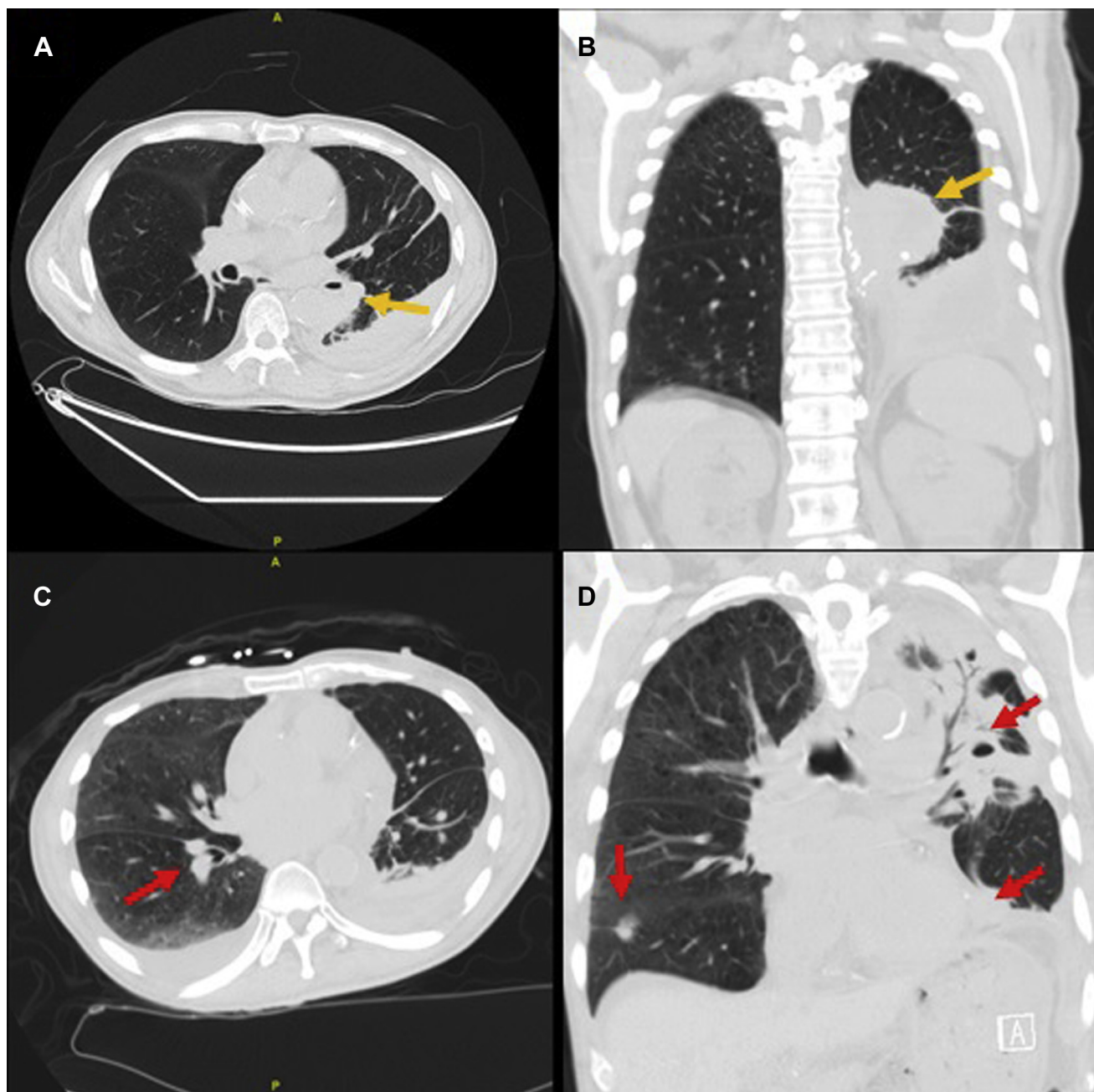
the primary mass was found, a new 7.6 cm mass in the posterior left lung base, which had invaded the adjacent pleura and pericardium, had developed. Additional subcentimeter nodules were also found in the right lung, along with growth of the adrenal mass and multiple new osseous lesions throughout the body. Although the disease progressed, its rate of growth was significantly lower and there was improvement in several of the metastatic sites. After an extensive discussion with the patient, it was decided to proceed with a third cycle of the chemotherapy.

One month later, he developed progressive dyspnea and chest pain. A repeat CT scan revealed steady progression of the disease with enlargement in both the lung and adrenal masses (Fig. 2A and B). Cell-free DNA analysis revealed positive findings for nontargetable mutations, including FGFR3-TAC03 fusion, PIK3CA amplification, and TP53 E287. Given the chemotherapy resistance and minimal intervention with the previous immunotherapy, it was decided to attempt a second trial of immunotherapy with atezolizumab. However, after 1 cycle, he was readmitted for confusion, lethargy, weakness, shortness of breath, hypercalcemia of the malignancy, and pneumonia. He developed acute hypoxic and hypercapnic respiratory failure that required endotracheal intubation and mechanical ventilation. A chest CT scan now revealed rapid enlargement of the primary mass, innumerable nodules, significant growth of the existing nodules, and extensive peritoneal involvement; all of which at a faster rate than the scans indicated during chemotherapy (Fig. 2C and D). Given his performance status, he was not a candidate for further therapy, and it was decided to proceed with hospice care 10 months after the initial discovery of the mass.

## Discussion and Conclusions

Immune evasion is an evolutionary necessity developed by cancer cells to thrive in the body. Although traditional chemotherapy limits cellular division and growth, checkpoint inhibitors attempt to stop and reverse cancer-mediated immune suppression.<sup>3</sup> As new treatment options become available, new patterns of disease behavior are manifesting.

Though anecdotally reported in the literature, HPD was first defined by Champiat et al.<sup>4</sup> as a twofold or greater increase in tumor growth rate (TGR) compared with pretreatment and progression as evaluated by the Response Evaluation Criteria in Solid Tumors. Although theoretically a sound definition, the subtleties of TGR vary among different studies; some frequently used definitions are as follows: the sum of the longest diameters of the target lesions,<sup>4,5</sup> the change in the diameter of the target lesions,<sup>6</sup> tumor volume,<sup>7</sup> or time-to-treatment failure, total tumor burden, or increase in progression pace.<sup>8,9</sup>



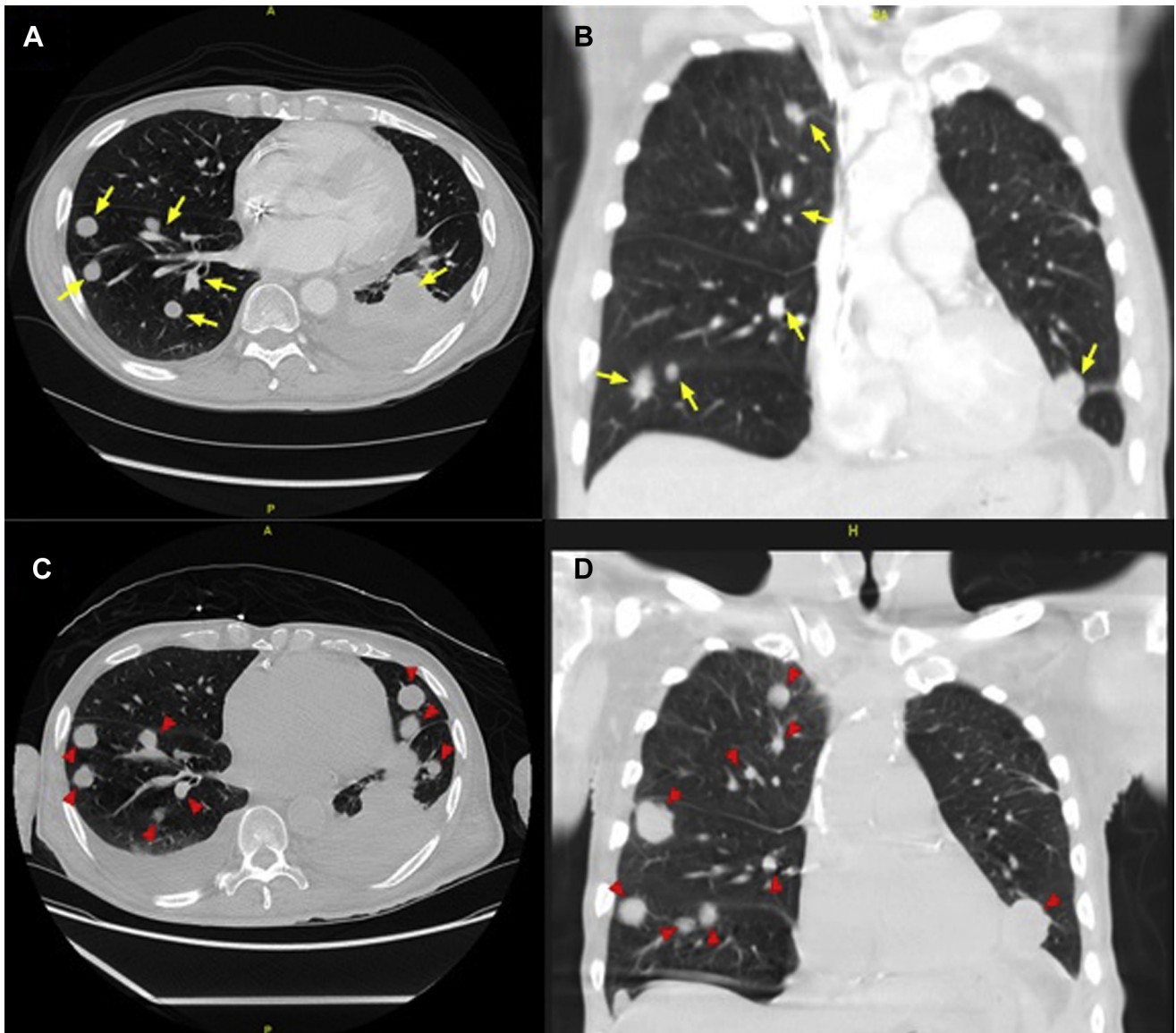
**Figure 1.** (A) Axial and (B) coronal views of the noncontrast computed tomography scan images before the initiation of pembrolizumab. [Yellow Arrow] A 5-cm mass-like area in the superior segment of the left lower lobe can be seen. (C) Axial and (D) coronal views of the noncontrast computed tomography scan images 3 months later (3 weeks after his first and only dose of pembrolizumab). [Red Arrow] Progression of the disease now at 10.8 cm in size and with new right lower lobe nodules.

Regardless of the definition used, the clinical phenomenon is unchanged: rapid progression of the disease while on ICI. The incidence of this paradoxical phenomenon also varies among study results ranging from 4% to 15% in mixed solid tumors, 8% to 21% in NSCLC, and 29% in head and neck cancers.<sup>4,5</sup> Contributing clinical factors, such as age more than 65 years, a higher number of metastatic lesions at diagnosis, and locoregional disease recurrence, have been reported but should be considered with caution

because they have not been used consistently in all analyses. Interestingly, PD-L1 expression, number of previous therapies, and advanced stage, or poor performance status at baseline have not been linked to HPD.<sup>4</sup> The manifestation of HPD is associated with a poorer overall survival in retrospective and prospective trials<sup>5</sup> and may explain why some phase III clinical trials were terminated early.<sup>7</sup>

There are increasing data from retrospective studies arguing in favor of HPD.<sup>10</sup> A study by Ferrara et al.<sup>7</sup>





**Figure 2.** (A) Axial and (B) coronal view contrast CT after 3 cycles of carboplatin and paclitaxel, revealing further progression of the disease with enlarging mass and [Yellow Arrow] increased number of pulmonary nodules. (C) Axial and (D) coronal view of the noncontrast CT scan 5 weeks later (2 weeks post atezolizumab infusion) showing [Red Arrow] increasing in both size and number of lung lesions.

analyzed a cohort of pretreated patients with advanced NSCLC who received programmed cell death protein-1 (PD-1)/PD-L1 inhibitors or single-agent chemotherapy and assessed the rate of HPD in both groups by calculating TGR before and during treatment. HPD was noted in 13.8% of the patients treated with ICIs compared with 5.1% of the patients treated with chemotherapy. Their definition of HPD included tumor growth of more than 10% per month before ICIs and more than 60% after therapy, or more than 80% per month after therapy if tumor growth was 30% before ICIs. The inclusion of these strict criteria supports a negative effect of PD-1/PD-L1 inhibition instead of progression, which could solely be explained by the natural history of the disease. Other

authors argue against the existence of this phenomenon. Pearson et al.<sup>11</sup> cite the lack of placebo-controlled cohort studies as one of the reasons that HPD cannot be adequately described; they also argue that the crossing of survival curves found in the clinical trials does not reveal a change in TGR but rather more of disease control with chemotherapy than with ICIs. In addition, a biological basis for HPD has not been fully described yet.

Nevertheless, several preclinical studies have formulated various hypotheses with postulated pathophysiology. These are dutifully summarized in the review by Champiat et al.<sup>4</sup> The proposed mechanisms include the following: T regulatory cell expansions secondary to checkpoint blockade leading to immune suppression;

increased T-cell exhaustion owing to alternative checkpoint pathways; checkpoint blockade resulting in immunosuppressive cytokine release from macrophages, dendritic cells, or other myeloid-derived cells; an uncontrolled inflammatory response; and direct activation of oncogenic pathways by the checkpoint blockade.<sup>10</sup> The actual cause is likely a combination of these pathways along with yet other unrecognized cell processes. Even though the association between HPD and ICIs must still be clearly defined, it is difficult to ignore the data and reports that reveal that a group of patients treated with ICIs had accelerated progression and poor outcomes.

Our patient was diagnosed with an aggressive squamous cell lung carcinoma. The initial CT scan after his COPD exacerbation revealed a 4 cm × 5 cm × 5 cm mass in the left lower lobe. The PET with CT scan done approximately 3 weeks later revealed a similar-sized mass along with the initial metastatic sites in the left pleura, pleural effusion, and the right adrenal gland. He tolerated the research protocol and had no major issues for 6 weeks until immunotherapy administration. Three weeks after administration of pembrolizumab, the imaging revealed that the primary mass had nearly doubled in size, the adrenal mass had enlarged, and several new right-sided pulmonary nodules had developed. There was a profound change in the tumor burden, and it was decided to stop the immunotherapy. Traditional cytotoxic chemotherapy reduced the size of the primary mass but he had stable disease progression. The use of atezolizumab resulted in yet another HPD as revealed by imaging a few weeks later, with innumerable lung nodules, significant growth in all previous metastatic sites and the primary site, and significant worsening of pleural and peritoneal involvement, all at a rate that was markedly worse than that of the stable disease progression found during traditional chemotherapy.

To our knowledge, this is the first reported case of a significant progression after treatment with 2 different ICIs on different occasions. The temporal relation between tumor progression and decline in performance status supports and argues in favor of the existence of HPD after PD-1/PD-L1 inhibition. As checkpoint inhibitors become a major treatment option for many cancers, the phenomenon of HPD must be considered as a possible outcome and studied further to determine who would be at risk. Furthermore, the presence of HPD after a single exposure to a checkpoint inhibitor suggests the preclusion of all future checkpoint inhibitors.

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