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CASE REPORT

Metastatic Clear Cell Renal Cell Carcinoma with Hyperprogressive Disease after Anti–Programmed Death-1 Immunotherapy: A Case Report

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INTRODUCTION

Immunotherapy has recently achieved dramatic success in the treatment of a wide variety of cancers. With the identification of programmed death-1 (PD-1) and its ligand PD-L1 playing a key role in tumour immune escape and cancer growth, immune checkpoint inhibitors that block the PD-1/PD-L1 pathway have been studied and demonstrated significant benefit in clinical trials.

Renal cell carcinoma (RCC) has long been recognised as an immunologically sensitive tumour with a distinctive response to high-dose interleukin-2 and interferon-α. In the CheckMate025 randomised phase 3 study, nivolumab, an immunoglobulin G4 monoclonal antibody against PD-1, was shown to improve the response rate and overall survival in patients with advanced RCC who were previously treated with one or more antiangiogenic agents compared with everolimus.[1-3] Heterogeneous post-treatment response patterns are observed during immunotherapy.[4] In addition to conventional response patterns, hyperprogressive disease (HPD) is a novel observation. We report a case of metastatic clear cell RCC (ccRCC) presenting with this novel aggressive phenomenon during the initial phase of immunotherapy.

CASE REPORT

A 64-year-old woman with good past health presented with gross haematuria in March 2016. Computed tomography (CT) urogram revealed a left renal mass measuring 11.4 cm with heterogeneous contrast enhancement. There were also multiple enlarged lymph nodes over the left renal hilum and para-aortic region as well as multiple lung nodules (Figure 1). CT-guided fine needle aspiration of the lung nodule in the right lower lobe confirmed ccRCC with immunostaining positive for AE1/3 and CD10, and negative for CK7, CD117, 34BE12, and TTF-1.

Debulking nephrectomy was not recommended due to her high operative risk. In June 2016, the patient was treated with pazopanib and in September 2016, interval CT scan showed stable disease. In December 2016, interval contrast CT scan revealed mild interval increase in size of the left renal tumour. Most metastatic lymphadenopathies and lung nodules also showed interval enlargement. A new metastasis was seen in segment VII of the liver and ascites was noted.

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Ethics Approval: This study was conducted in accordance with the Declaration of Helsinki. The patient provided informed consent for all procedures.

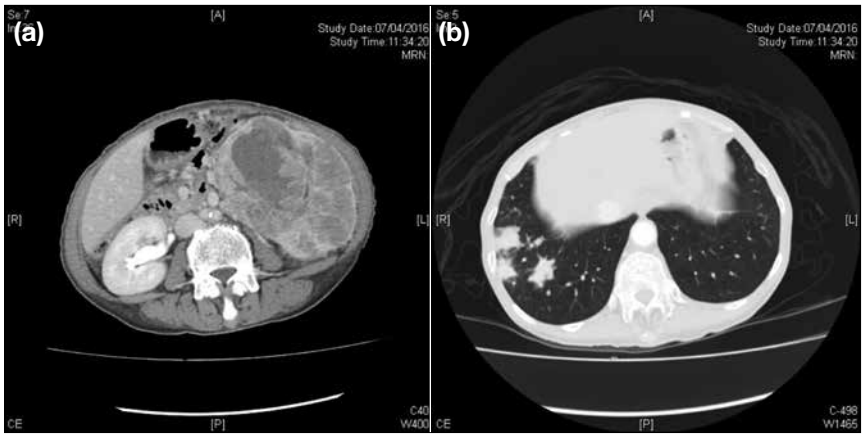

Figure 1. A 64-year-old woman with clear cell renal cell carcinoma. (a and b) Diagnostic contrast computed tomography images showing a 11.4-cm left renal mass with regional lymphadenopathy and lung metastases.

Second-line treatment with axitinib was started in January 2017. Progress contrast CT scan at 9 days before treatment showed disease progression again with increase in size of the renal tumour. The lung nodules had also increased in size and extent, especially over the bilateral lower lobes and there was interval enlargement of the multiple metastatic lymphadenopathies. The liver metastasis in segments VII and VIII were more conspicuous and new peritoneal deposits were noted.

In April 2017, the patient received 3 mg/kg nivolumab. At 5 days after nivolumab administration, the patient reported dyspnoea, lethargy, and poor appetite and was admitted through the emergency department to a general medical unit of a hospital near her home. She required the use of 15-L O_2 therapy. On admission, the patient's C-reactive protein level was 18.9 mg/L (reference, ≤5 mg/L) and her white cell count was 13.53 × 10^9/L (normal range: 3.7-9.3 × 10^9/L; her baseline white cell count was normal). At 6 days after nivolumab administration, urgent contrast CT thorax was performed to exclude pulmonary embolism. Although no pulmonary embolism was evident, multiple patchy opacities as consolidations and multiple nodules in both lung fields showed dramatic increase in size and extent, especially over the bilateral lower lobes and the left upper lobe. Ground-glass opacities in both lungs were also seen (Figure 2). Given the drastic and rapid change in CT findings in both lungs (Table 1), the CT findings could represent pneumonitis associated with the treatment with a differential diagnosis of disease progression. The previously seen prominent-to-enlarged metastatic lymphadenopathies showed interval enlargement and increase in extent.

Her clinical condition deteriorated rapidly despite administration of intravenous antibiotics and she finally succumbed due to respiratory failure 7 days after nivolumab administration.

DISCUSSION

Although immune checkpoint blockade has emerged as a principal treatment modality for many cancers, it has been recognised that disease response and stabilisation can occur after an initial paradoxical increase in tumour burden or appearance of new lesions, indicating pseudoprogression.

HPD is a newly recognised condition where tumour growth is accelerated by immunotherapy with consequent rapid disease progression. Under these circumstances, continuation of treatment may be considered unsafe. There is no consensus on the definition of HPD but quantifying the progression rate with tumour growth rate (TGR) may enable more objective elucidation of the condition. HPD has been previously been defined as RECIST (response evaluation criteria in solid tumours) disease progression with ≥2-fold increase in TGR from baseline before treatment.[5-7]

A study that included 131 evaluable patients treated with anti-PD-1/PD-L1 reported a 9% incidence of HPD. Among the nine patients diagnosed with renal cancer, none developed HPD.[5] In another study that included 34 head and neck cancer patients treated with PD-1/PD-L1 inhibitors, the incidence of HPD was 29%.[6] In clinical studies reporting HPD following use of anti-PD-1/PD-L1+/- CTLA4 (cytotoxic T-lymphocyte associated antigen 4), HPD was consistently associated with worse clinical outcomes (Table 2).[5-8]

Previous studies used the sum of the longest diameter of target lesions to calculate TGR. In this case report, we used three-dimensional parameters to record TGR. We

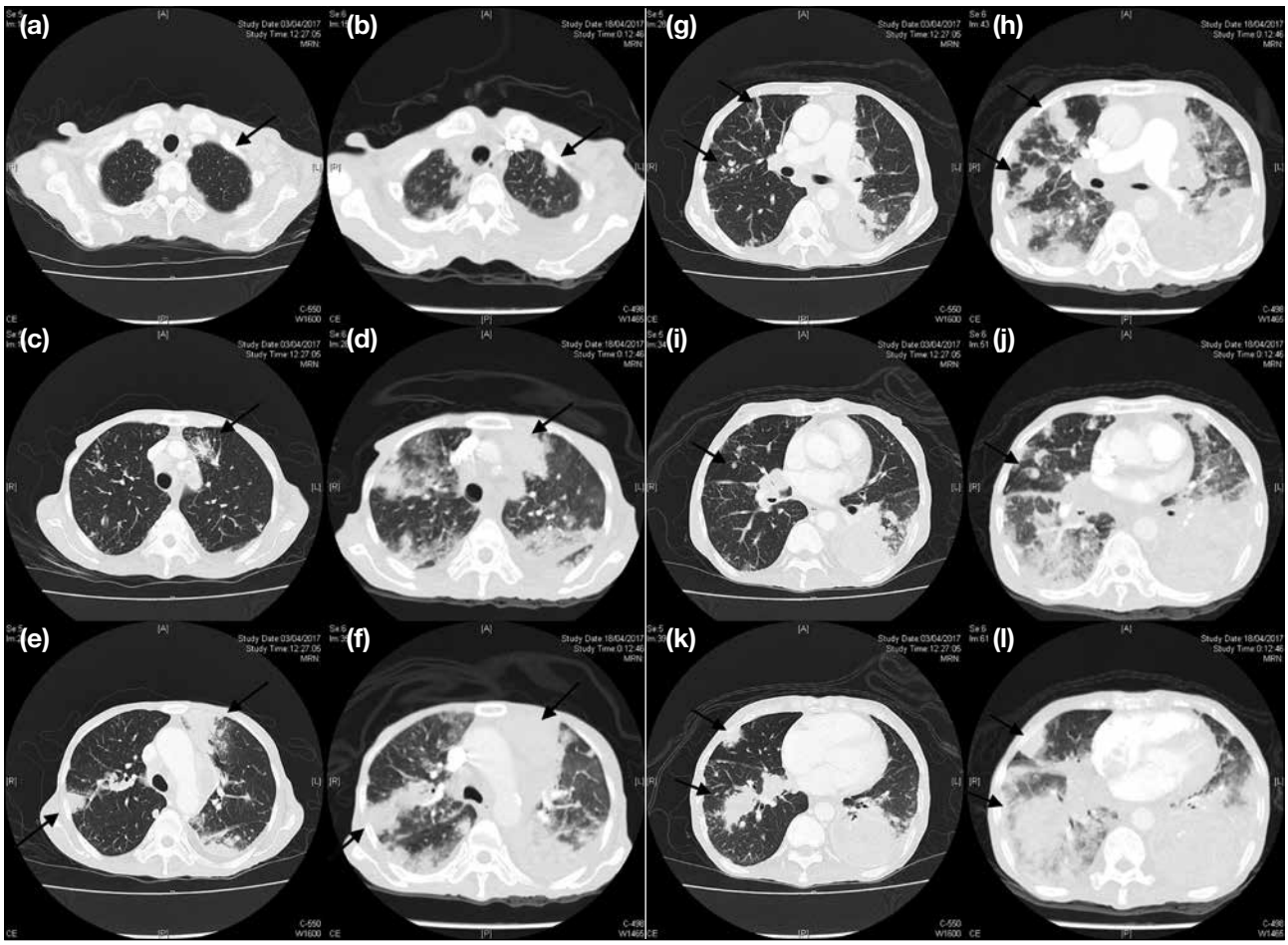

Figure 2. The same 64-year-old woman with clear cell renal cell carcinoma. Arrows in contrast computed tomography images show (a, b) interval development of new lung metastasis, (c, d) interval increase in size of patchy consolidation in sites of metastasis; (e, f) interval increase in size of lung metastasis and development of new consolidative changes; and (g to l) interval increase in size of lung metastasis.

Table 1. Serial tumour burden in volume, TGR, and TGKR (ie, the ratio of TGR before and after treatment) for a 64-year-old woman with clear cell renal cell carcinoma who underwent nivolumab treatment in April 2017.

	Date of progress CT		
	Initial presentation (Dec 2016)	9 days before treatment (Apr 2017)	6 days after treatment (Apr 2017)
Tumour volume (cm^3)	60.57	474.91	1876.75
TGR (cm^3/day)	4.06	93.46 cm^3/day	
TGKR		23.0	

Abbreviations: CT = computed tomography; TGKR = tumour growth kinetics ratio; TGR = tumour growth rate.

imported serial progress CT images into the radiotherapy planning system Varian™ and contoured all the intra-thoracic measurable target lesions. Measurable target lesions were defined as tumour deposits with diameter >1 cm. Tumour volume was calculated by computer. Table 1 summarises the change in tumour volume and TGR before and after treatment. A 23-fold increase in TGR after nivolumab administration was evident. This phenomenon of significant disease progression with more than doubling of tumour growth rate is known as HPD.

The mechanism of HPD is unclear. Kato et al[7] identified the potential role of genomic analysis and demonstrated that MDM2 amplification or EGFR aberrations may be associated with poor clinical outcome.

Since anti-PD1 immunotherapy reactivates cytotoxic T cells to enhance their tumouricidal action, massive infiltration of immune cells into the tumour may explain the rapid radiological disease progression, as evidenced by biopsy results of metastatic melanoma in another case report that showed similar findings.[9] Tumour necrosis, deemed to be one of the causes of pseudoprogression, may also play a role in hyperprogression.[10]

In this case report, there are some limitations to our analysis. First, there was no subsequent imaging

Table 2. Summary of data on hyperprogressive disease.

Study (first author)	Study design	Patient group	HPD definition	Results
Champiat[5]	Retrospective study	218 patients at Gustave Roussy Institute treated with anti-PD-1/PD-L1	RECIST progression at the first evaluation and a ≥2-fold increase of the TGR	HPD is observed in 9% of patients. HPD is associated with higher age and decreased OS. TGR (baseline before treatment) is inversely correlated with response to anti-PD-1/PD-L1 therapy.
Saâda-bouzid[6]	Retrospective study	34 patients of metastatic HNSCC treated with anti-PD-L1/PD-1 agents	TGKR ≥2 (TGKR, ratio of the slope of tumour growth before treatment and the slope of tumour growth on treatment)	HPD is observed in 29% of patients and is associated with decreased PFS.
Kato[7]	Retrospective study	155 stage IV cancer patients treated with immunotherapies including CTLA-4, PD-1/PD-L1 inhibitors or other investigational agents.	Time-to-treatment failure <2 months, >50% increase in tumour burden compared imaging before immunotherapy, and >2-fold increase in progression pace.	HPD after PD-1/PD-L1 is associated with MDM2 family amplification or EGFR aberrations. HPD is associated with poor clinical outcome.
Kobari[8]	Case report	3 patients of mRCC treated with nivolumab	Not defined	HPD is observed in mRCC.

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen 4; HNSCC = head and neck squamous cell carcinoma; HPD = hyperprogressive disease; mRCC = metastatic renal cell carcinoma; OS = overall survival; PD1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; TGR = tumour growth rate.

after disease progression to fulfil the definition of "progressive disease" under irRC. Second, there was no pathological correlation since no biopsy was performed to demonstrate radiological pneumonitic changes and disease progression. Third, TGR was calculated based only on intrathoracic tumour burden since only CT thorax was performed after nivolumab administration. Fourth, the time between baseline scan and the previous scan was 5 months. As such, TGR before treatment may have been underestimated since rapid tumour growth may have occurred just prior to the baseline scan.

HPD is a newly recognised disease response pattern during immunotherapy. It is characterised by accelerated TGR during the initial phase of treatment. Clinicians should be aware of this potentially lethal phenomenon, particularly in patients with extensive visceral metastases. Currently there are few studies of HPD. The phenomenon is observed across metastatic non-small cell lung cancer, head and neck squamous cell carcinoma, and ccRCC. More studies are needed to clarify the implications of this phenomenon and the associated underlying biogenetics. This may provide insight into more personalised oncological treatment in future.

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