


## Case Report

# Rapidly progressing programmed cell death 1 inhibitor-related pneumonitis in a hemodialytic patient with metastatic renal cell carcinoma

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### Abbreviations & Acronyms

AIP = acute interstitial pneumonia  
CT = computed tomography  
DAD = diffuse alveolar damage  
EGFR = epidermal growth factor receptor  
HD = hemodialysis  
IP = interstitial pneumonitis  
irAE = immune-related adverse event  
mTOR = mammalian target of rapamycin  
PD-1 = programmed cell death 1  
RBC = red blood cell  
RCC = renal cell carcinoma  
VEGF = vascular endothelial growth factor  
WBC = white blood cell

**Introduction:** The efficacy and safety of nivolumab for patients receiving hemodialysis remain uncertain. Herein, we report a patient receiving a maintenance hemodialysis with life-threatening interstitial pneumonitis caused by nivolumab for metastatic renal cell carcinoma.

**Case presentation:** A 61-year-old man with chronic kidney disease after nephrectomy for renal cell carcinoma was started on hemodialysis. Six months later, he developed multiple bone metastases and received pazopanib. Pazopanib, however, was not effective. We then switched to nivolumab as second-line treatment. Five days after the first administration of nivolumab, he complained of respiratory discomfort and malaise with oxygen desaturation. Chest computed tomography demonstrated diffuse areas of ground glass opacity in both lung fields, suggesting programmed cell death 1 inhibitor-related pneumonitis. Prompt corticosteroid therapy led to improvement of the symptoms.

**Conclusion:** Caution should be exercised on the administration of nivolumab to hemodialysis patients due to the risk of interstitial pneumonitis.

**Key words:** HD patients, metastatic renal cell carcinoma, nivolumab, PD-1 inhibitor-related pneumonitis.

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## Keynote message

The administration of nivolumab to HD patients with metastatic RCC may occasionally cause serious adverse effects. The present case developed life-threatening IP. The administration of nivolumab to HD patients should be conducted cautiously due to the risk of respiratory failure.

## Introduction

Nivolumab is a fully human immunoglobulin four monoclonal antibody that targets PD-1, one of the T-cell surface membrane receptors. A phase 3 study showed that nivolumab is superior to everolimus in terms of overall survival and adverse events in patients with metastatic or inoperative RCC for 1 or 2 lines of failed VEGF-targeted therapy.<sup>1</sup> On the other hand, immune-mediated adverse events have been reported in some patients receiving nivolumab.<sup>1,2</sup>

To our knowledge, there are few published data on the safety and efficacy of PD-1 inhibitors in hemodialytic patients. We report a case of rapidly progressing PD-1 inhibitor-related pneumonitis in a hemodialytic patient with metastatic RCC.

## Case presentation

A 61-year-old man with hypertension, hyperlipidemia, and chronic kidney disease underwent retroperitoneal right nephrectomy for a 6.5-cm renal mass. The histological diagnosis was

**Table 1** Laboratory data on the 5th day after nivolumab

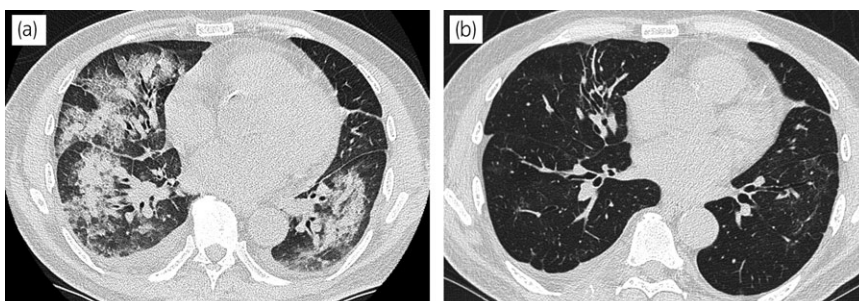
Hematological examination		
WBC	8000/ $\mu$ L	
Band	3.5%	
Seg	93.5%	
Eosino	0%	
Lympho	2%	
Mono	1%	
RBC	$312 \times 10^4/\mu$ L	
Hb	10 g/dL	
Ht	31%	
Plt	$21.9 \times 10^4/\mu$ L	
CRP	35.7 mg/dL	
BUN	73.4 mg/dL	
Cr	12.8 mg/dL	
LDH	233 U/L	
ALP	245 U/L	
$\gamma$ -GTP	77 U/L	
Glu	102 mg/dL	
Na	126 mmol/L	
K	5.9 mmol/L	
Cl	89 mmol/L	
Ca	8.6 mg/dL	
IP	5.9 mg/dL	
Arterial blood gas test (O <sub>2</sub> 5L)		Normal value
pH	7.43	
PO <sub>2</sub>	67 mmHg	80–100
PCO <sub>2</sub>	38 mmHg	35–45
ABE	0.9 nmol/L	–2–2
HCO <sub>3</sub>	25.2 nmol/L	22–26
SpO <sub>2</sub>	93.1%	92–98.5
S-IL-2R	8321 U/mL	122–496
B-D glucan	3.4 pg/mL	11.0 or less
Aspergillus antigens	0.1 (–)	
Auto immune disease		
Anti-nuclear antibody	40 times	<40 times
Homogeneous	40 times	<40 times
Speckled	40 times	<40 times
Anti-Jo-1 antibody	Negative	
PR3-ANCA	<1.0	<1.0
MPO-ANCA	<1.0	<1.0
Anti-GBM antibody	<2.0	<2.0
Interstitial pneumonitis		
KL-6	278 U/mL	<500
SP-D	222 ng/mL	<110

clear cell carcinoma, G2 (Fuhrman), INFa, v1, ly0, eg, fc1, im0, rc-inf0, rp-inf1, s-inf1, pT3a with infiltration of the renal sinus. The progression of chronic kidney disease necessitated

HD after nephrectomy. Nevertheless, 6 months later, he developed multiple bone metastases including the 5th, 6th, and 8th ribs, the 9th thoracic vertebra, and 2nd lumbar vertebra. Pazopanib was initiated at a half of the standard dose (400 mg/day) as first-treatment for metastatic RCC. Six months after the induction of pazopanib, rapid progression of bone metastasis was noted. As second-line treatment for metastatic RCC, nivolumab was started at the standard dose (3 mg/kg). On the 2nd day after the first administration of nivolumab, chest X-ray did not show any abnormal shadows in spite of fever and general fatigue. On the 5th day, he complained of discomfort on breathing and fatigue with oxygen desaturation. Chest CT on the 5th day demonstrated diffuse ground glass opacity in both lung fields, suggesting nivolumab-induced pneumonitis with the AIP/DAD pattern (Fig. 1a). Blood examination on the 5th day showed high levels of CRP, s-IL-2R, and SP-D, indicating interstitial lung disease (Table 1). In addition, a normal WBC count and negative results in a sputum culture test for B-D glucan and Aspergillus antigen ruled out bacterial or atypical pneumonia. A normal level of anti-nuclear antibody and presence of ANCA antigens excluded connective tissue diseases. The bronchoscope was not conducted because the patient refused. The patient was diagnosed with PD-1 inhibitor-related IP. Intravenous corticosteroid therapy (methylprednisolone at 1 g/day for 3 days) with adjunctive antibiotics led to rapid recovery. On the 9th day, oral corticosteroid was started, and then slowly tapered. On the 22nd day, chest CT showed improved opacity (Fig. 1b), and the patient was discharged on the 24th day. After recovery from PD-1 inhibitor-related IP, the patient refused our recommendation of axitinib as third-line therapy and selected palliative treatment.

## Discussion

The number of HD patients in Japan has been increasing, presently exceeding 300 000 people.<sup>3</sup> It is well-known that HD patients have a high incidence of RCC. Accordingly, the number of HD patients suffering from RCC has been increasing. The biology of RCC in HD patients has clinical and pathological characteristics.<sup>4</sup> HD patients were excluded from the prospective clinical trials such as Checkmate 025<sup>1</sup> and Checkmate 057.<sup>2</sup> To our knowledge, only a few reports<sup>5,6</sup> on the safety and efficacy of PD-1 inhibitors in HD patients were have been published. Tabei *et al.*<sup>5</sup> reported that in an HD patient with metastatic RCC nivolumab led to marked improvement without adverse effects in 4 weeks. Carlo and



**Fig. 1** (a) Chest CT on the 5th day after the first administration of nivolumab. Diffuse ground glass opacity in both lung fields was observed, suggesting nivolumab-induced pneumonitis with the AIP/DAD pattern. (b) Chest CT after steroid therapy on the 22nd day. Improved opacity was noted.

Feldman<sup>6</sup> reported an HD patient with metastatic RCC, in whom nivolumab led to hypercarbic respiratory failure possibly caused by multifactors such as diaphragmatic paralysis from pleural pseudoprogression, pneumonia, and heart failure 2 weeks after nivolumab administration. Because HD patients tend to have many comorbidities related to respiratory failure, which are confusing to irAE including IP. Therefore, HD patients treated with nivolumab need to be received intensive observation to prevent from irAE.

IP is a disease that affects the parenchyma or alveolar regions of the lung. Various drugs including antineoplastic therapies have the potential to cause IP, especially molecular-targeted agents, including EGFR-tyrosine kinase inhibitors such as gefitinib and mTOR inhibitors such as everolimus have reportedly caused a high incidence of IP.<sup>7</sup> Immune checkpoint blockade by PD-1 inhibitors is associated with unique toxicities, termed “irAEs,” which can involve different organs throughout the body. Among the irAEs, IP is relatively rare but clinically serious, and potentially life-threatening. The incidence of IP in RCC treated with PD-1 inhibitor was 4.1%.<sup>8</sup> The incidence of PD-1 inhibitor-related IP was higher in non-squamous cell lung cancer and RCC than melanoma.<sup>8</sup> PD-1 inhibitor-related IP can be inferred from CT findings and symptoms.<sup>9</sup> PD-1 inhibitor-related IP is known to respond to steroids. Corticosteroid was effective in the present case. According to information on nivolumab, higher risk factors for IP are as follows: a performance score  $\geq 3$ , pulmonary diseases such as interstitial pneumonia and pneumoconiosis, and autoimmune disease.<sup>10</sup> However, there is no description for patients with an impaired renal function, especially for dialytic patients. HD patients might be more susceptible to anti-PD-1-related adverse events because of not only an impaired renal function but also an immune-intolerance.

According to pharmacokinetic studies, the renal function did not affect nivolumab clearance, and the package insert does not recommend dose adjustments for chronic kidney disease.<sup>10</sup> Considering its high-molecular weight, nivolumab may not be cleared by HD. Nevertheless, without documented safety or efficacy in HD patients, oncologists might be reluctant to administer nivolumab for this patient population. This is particularly important because patients with RCC are common among those with an impaired renal function. Recently, the

combination therapy of ipilimumab and nivolumab started in patients with metastatic RCC as the first line,<sup>11</sup> therefore, the importance of irAE is expected to further increase.

In conclusion, the administration of nivolumab to HD patients with metastatic RCC may occasionally cause serious adverse effects. The present case developed life-threatening IP. The administration of nivolumab to HD patients might be conducted cautiously due to the risk of respiratory failure. We should accumulate more patients administered nivolumab with an impaired renal function, especially those receiving maintenance HD.

## Conflict of interest

The authors declare no conflict of interest.

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