



Two cases of anaphylaxis due to contrast media during administration of nivolumab and ipilimumab in metastatic renal cell carcinoma

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Abstract

A combination therapy of nivolumab and ipilimumab is effective for advanced renal cell carcinoma, but there are concerns about immune-related adverse events. A 46-year-old man was hospitalized for metastatic renal cell carcinoma. On day 9, he received nivolumab and ipilimumab. On days 16 and 49, he presented with fever, skin rash, and hypotension after contrast-enhanced computed tomography. A 70-year-old man was hospitalized for metastatic renal cell carcinoma. On day 9, he received nivolumab and ipilimumab. On day 44, he presented with fever, skin rash, and hypotension after contrast-enhanced computed tomography. Both patients were diagnosed with anaphylaxis due to the contrast agent.

Keywords Renal cell carcinoma · Nivolumab · Ipilimumab · Contrast agent allergy · Anaphylaxis · Immune-related adverse event

Introduction

Immune checkpoint inhibitors such as the anti-PD-1 antibody nivolumab and the anti-CTLA-4 antibody ipilimumab are currently used clinically for metastatic renal cell carcinoma. There is growing evidence that immune checkpoint inhibitors improve overall survival of patients with metastatic renal cell carcinoma. In the CheckMate-241 trial, first-line combination therapy of nivolumab and ipilimumab showed good results for advanced renal cell carcinoma [1]. In the CheckMate-025 study, second-line nivolumab showed good results for advanced renal cell carcinoma [2]. However, immunotherapy might result in immune-related adverse events (irAEs), owing to the activation of the immune system.

Allergies after non-ionic contrast-enhanced computed tomography (CECT) are uncommon, with an incidence of 0.7–3.1%, and incidence of severe allergy with hypotension at 0.02–0.04% [3]. Ridolfi et al. reported that, of 59 patients receiving ipilimumab, 7 patients developed CECT-related immediate adverse reactions [4]. However, reports about

this issue are limited, and the association between immune checkpoint inhibitors and CECT-related allergy remains unclear.

Herein, we report two cases of anaphylactic shock due to CECT during first-line combination therapy of nivolumab and ipilimumab for advanced renal cell carcinoma. To the best of our knowledge, this is the first report of anaphylaxis as a suspected irAE due to CECT allergy.

Case report

Case 1

A 46-year-old man was hospitalized owing to abdominal distension and weight loss in the past 1 month. He was born healthy and had no apparent allergic predisposition at the time of admission. CECT and renal biopsy revealed a 15-cm clear-cell renal cell carcinoma and multiple bone metastases (Fig. 1a, b). His Karnofsky performance score was 80. Laboratory examination revealed a hemoglobin level of 11.8 g/dL, platelet count of $504 \times 10^3/\mu\text{L}$, neutrophil count of $5280/\mu\text{L}$, corrected calcium of 15.7 mg/dL, and CRP level of 4.63 mg/L. The prognostic category of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) was “poor risk.” Nivolumab and ipilimumab were administered on day 9 of hospitalization, along

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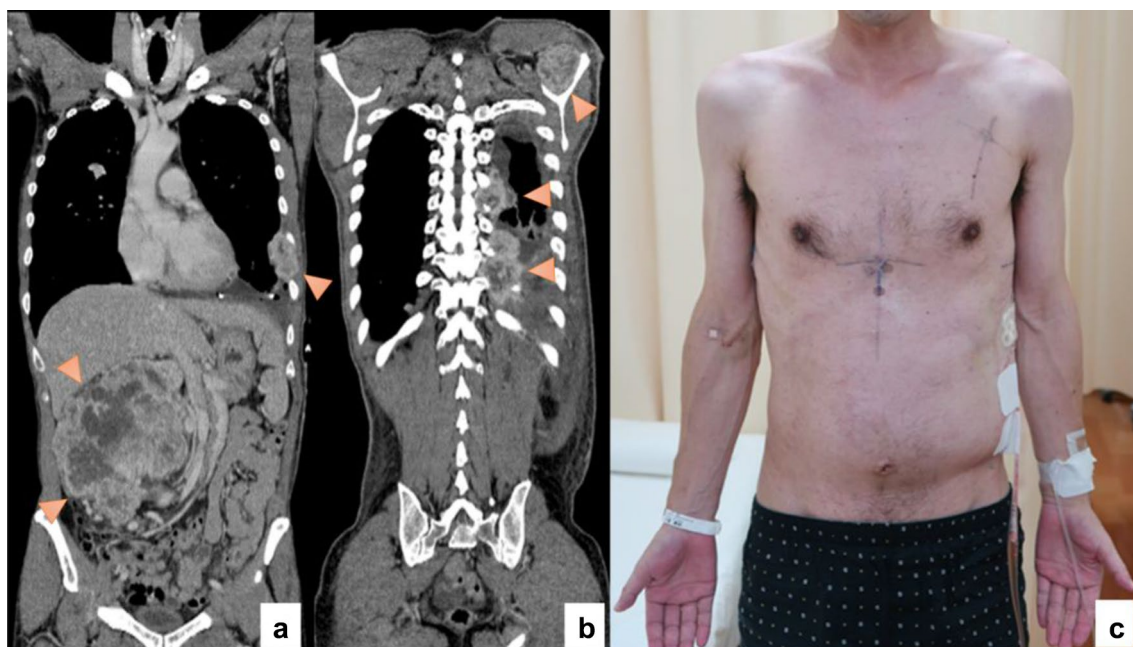


Fig. 1 **a** On day 1, contrast-enhanced computed tomography (CECT) in the coronal plane revealed a 15-cm right renal mass and bone metastases (arrow). **b** CECT on day 1 revealed multiple thoracic

vertebral metastases and scapular metastasis (arrow). **c** On day 17, images revealed mild skin rash after CECT

with palliative radiation therapy of 37.5 Gy/15 fr to the thoracic vertebral metastasis. On days 16 and 49, the patient presented with fever, skin rash, and hypotension approximately 5 h after non-ionic CECT (Table 1 and Fig. 1c), along with abnormally elevated procalcitonin (PCT) levels (2.2 ng/ml on day 17 and 125.4 ng/ml on day 50), and a transient decrease in eosinophil count (30/ μ l on day 17 and 50/ μ l on day 49 and average of 400/ μ l on surrounding days). IgE level was not measured. All the blood culture results were negative, and CECT revealed no site of infection. We finally suspected CECT allergy after the second CECT on day 49 and administered 200 mg hydrocortisone sodium on day 50. Thereafter, the patient was stable and completed four courses of nivolumab and ipilimumab. He experienced tumor progression 2 months later. At that time, he switched

to post-treatment with axitinib; subsequently, the tumor shrank.

Case 2

A 70-year-old man was hospitalized for left inguinal pain in the past 6 months. CECT and renal biopsy revealed a 6-cm right clear-cell renal cell carcinoma and left iliac and thoracic vertebral metastases. Prior to admission, he was taking amlodipine and allopurinol for hypertension and hyperuricemia; however, he had no apparent allergic predisposition. His Karnofsky performance score was 60. Laboratory examination revealed a hemoglobin level of 16.1 g/dL, platelet count of $267 \times 10^3/\mu$ L, neutrophil count of 5580/ μ L, corrected calcium level of 10 mg/dL, and

Table 1 Parameters on admission day and on the days CECT was performed (Case 1)

	First CECT on admission day (day 1)	Day 9	Second CECT on day 16	Day 30	Third CECT on day 49
Physical findings			Skin rash		Skin rash
BT ($^{\circ}$ C)	37.3	37.4	39.9	37.7	40
BP (mmHg)	145/98	119/86	96/63	113/76	74/30
Medication		Nivolumab + ipilimumab		Nivolumab + ipilimumab	Noradrenaline
			Acetaminophen		Acetaminophen

CECT contrast-enhanced computed tomography, BT body temperature, BP blood pressure

CRP level of 0.91 mg/L. The IMDC prognostic category was “intermediate risk.” Nivolumab and ipilimumab were administered on hospitalization day 9; palliative radiation therapy of 37.5 Gy/15 fr was also administered to the thoracic vertebral and left iliac metastases (Fig. 2a, b). On day 44, the patient presented with fever, followed by skin rash and hypotension, which occurred within 2 and 5 h, respectively, after non-ionic CECT (Table 2; Fig. 2c), along with a transient decrease in eosinophil count (190/ μ l on day 44 and 0/ μ l on day 45 and average of 1000/ μ l on surrounding

days). IgE level was not measured. All blood culture results were negative, and CECT revealed no site of infection. As we suspected CECT-related allergy, we administered 300 mg hydrocortisone sodium on day 44. The patient completed four courses of nivolumab and ipilimumab. However, he presented with rash exacerbation during the fourth treatment course. Drug-induced hypersensitivity syndrome was suspected considering the medication history of oral allopurinol and high level of the serum titer for HHV-6 IgG antibody (IgM was < tenfold and IgG was 640-fold). The

Fig. 2 **a** On day 1, contrast-enhanced computed tomography (CECT) in the coronal plane revealed a 6-cm right renal mass and left iliac metastases (arrow). **b** CECT on day 1 revealed thoracic vertebral metastases (arrow). **c** On day 45, images revealed skin rash exacerbation after CECT

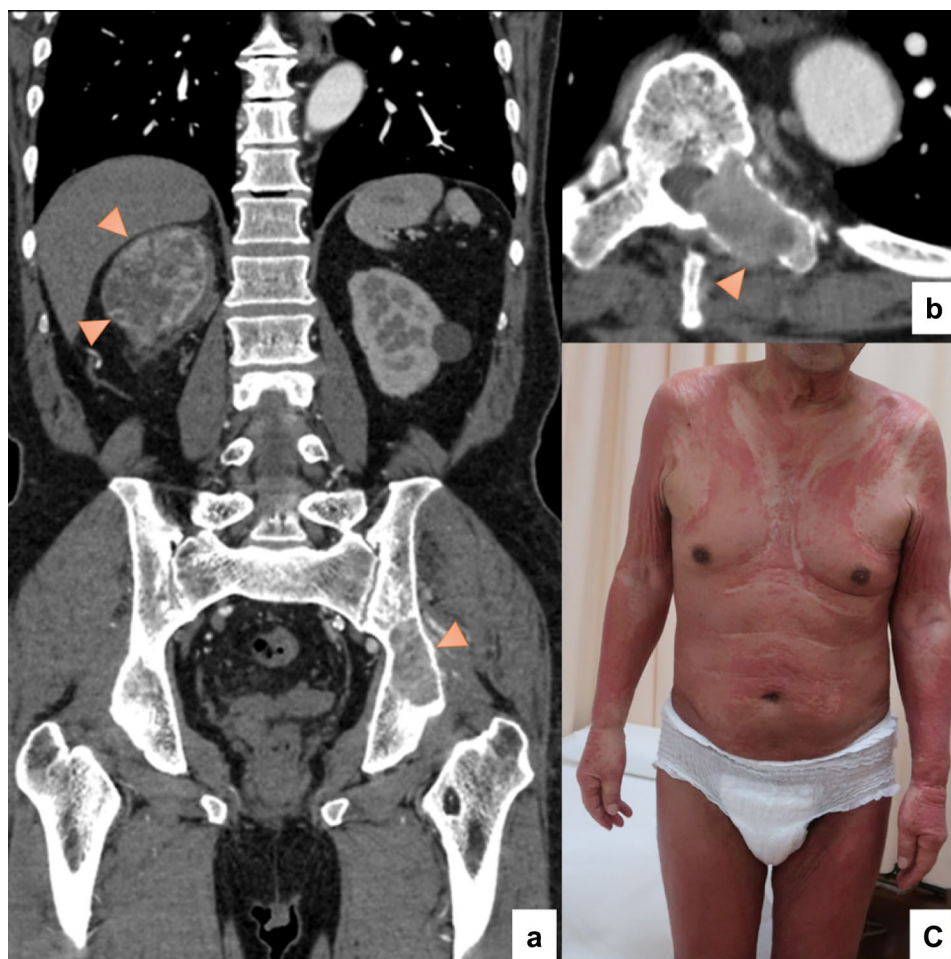


Table 2 Parameters on admission day and on the days CECT was performed (Case 2)

	First CECT on admission day (day 1)	Day 9	Day 32	Second CECT on day 44
Physical findings				Skin rash
BT (°C)	37.2	36.9	37.1	40.1
BP (mmHg)	127/69	135/80	94/54	68/48
Medication		Nivolumab + ipilimumab	Nivolumab + ipilimumab	Hydrocortisone sodium Noradrenaline

CECT contrast-enhanced computed tomography, BT body temperature, BP blood pressure

administration of steroids stabilized the patient's condition, and plain CT revealed partial response of the tumor.

Discussion

We encountered CECT allergy in two patients who received nivolumab and ipilimumab. First-line combination therapy of nivolumab and ipilimumab resulted in higher objective response rates and progression-free survival in patients with advanced renal carcinoma compared to molecular targeted drugs. However, the incidence of all grade 3 or 4 drug-related adverse events was 46% after first-line combination therapy of nivolumab and ipilimumab [1], and 19% after second-line treatment with nivolumab [2]. Combination therapy with nivolumab and ipilimumab is associated with an increased frequency of side effects as per data from other clinical trials [5]. For example, the frequency of rash was reported as 9–15% in a group treated with nivolumab alone; however, it was reported as 16.7–30% in the group treated with a combination therapy of nivolumab and ipilimumab [5]. Other side effects, such as fever and anaphylaxis, were not recorded in these clinical studies. Future studies should examine these side effects.

It has been recently reported that PD-1 suppresses allergen-specific CD4+ T cells, and blocking PD-1 strongly enhances the proliferation and cytokine production of allergen-specific CD4+ T cells [6]. These allergen-specific CD4+ T cells in turn cause type 1 allergies by inducing the production of IgE via IL4 secretion [7]. Blocking CTLA-4 affects the immune priming phase by supporting the activation and proliferation of effector T cells [8]. The exact mechanism by which nivolumab and ipilimumab causes anaphylaxis is not completely understood; however, both of them might be associated with the onset of anaphylaxis.

Both the patients had bulky tumors and multiple metastases. Sakata et al. reported that a high tumor burden was a risk factor for severe irAEs in patients who responded to immune checkpoint inhibitors [9]. We performed CECT to confirm whether the tumors had progressed. In addition, both patients had fever, hypotension, and skin rash after CECT (Tables 1, 2). The blood culture results were negative, and CECT revealed no obvious source of infection. As both Case 1 and Case 2 satisfied the diagnostic criteria of anaphylaxis given by Simon et al., we diagnosed both cases as anaphylaxis due to a contrast agent [10]. Moreover, as the condition of both patients improved in a few days, we continued treatment with nivolumab and ipilimumab.

PCT levels were abnormally high in Case 1, although there was no other evidence of infection. We believe that a strong increase in rapid oxidative stress by acetaminophen poisoning in addition to contrast agent anaphylaxis might have led to PCT overproduction [11]. It is worth noting that

laboratory data from samples collected from both patients during anaphylactic shock revealed a transient decrease in eosinophil count. This decrease may be attributable to the migration of eosinophils to tissues; however, to the best of our knowledge, no previous study has reported the possible underlying mechanism.

Allergic predispositions, such as atopic dermatitis and asthma, are known risk factors for anaphylaxis [9, 12]. Allergic additional effects such as rash might increase the risk of anaphylaxis during the administration of an immune checkpoint inhibitor. Both the patients did not have a record of allergic predisposition prior to nivolumab and ipilimumab administration; however, a mild rash was noted at the time of CECT. This finding suggests that it might be preferable not to use the CECT with patients who develop IrAE during combination therapy of nivolumab and ipilimumab, if it can be avoided. Nevertheless, at the time of writing, there is no established consensus regarding the optimum follow-up of patients with advanced renal cell carcinoma treated with immune checkpoint inhibitors. As a result, a continued accumulation of cases is required to clarify this issue.

In conclusion, immune checkpoint inhibitors are useful for treating advanced renal cell carcinoma. However, CECT during drug administration might induce contrast agent allergies. Therefore, physicians should be aware of contrast agent allergies, especially while administering first-line combination therapy of nivolumab and ipilimumab.

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Compliance with ethical standards

Conflict of interest The authors state that there are no known conflicts of interest.

Informed consent Informed consent was obtained from both the patients for publication of this case report and any accompanying images.

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