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Re-Challenging with Nivolumab in Metastatic Renal Cell Carcinoma After Immune-Related Interstitial Pneumonia: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 52-year-old
Final Diagnosis: Renal cell carcinoma
Symptoms: Cough
Medication: —
Clinical Procedure: —
Specialty: Urology

Objective: Unusual clinical course

Background: The efficacy and safety of re-challenge with immune checkpoint inhibitors after immune-related adverse events have not been established. We report a case of successful re-administration of nivolumab in metastatic renal cell carcinoma after discontinuation due to immune-related adverse events.

Case Report: Laparoscopic nephrectomy was performed on a 52-year-old man diagnosed with renal cell carcinoma pT1b-N0M0. After surgery, left adrenal and lung metastases appeared. Nivolumab was administered as a sixth-line therapy, and he achieved a partial response, but interstitial pneumonia occurred. He was diagnosed with grade 2 immune-related adverse events, and nivolumab treatment was discontinued. Interstitial pneumonia was well controlled by steroids. He maintained a partial response for a long time, and the lung metastases disappeared 7 months after discontinuation. However, bilateral lung metastases reappeared 10 months after the discontinuation. We decided to re-administer nivolumab, while carefully monitoring the patient and fully explaining the risk of recurrence of immune-related adverse events. After 5 cycles of re-administration, computed tomography revealed a reduction in metastases without re-activation of interstitial pneumonia. He experienced a grade 1 fever the day after re-administration, but continued nivolumab therapy without other adverse events. After 7 cycles of re-administration, the lung metastases increased, and nivolumab treatment was terminated. Two months later, a grade 2 interstitial pneumonia recurred, but improved rapidly with oral steroids.

Conclusions: For patients who have discontinued immune checkpoint inhibitors due to immune-related adverse events, re-challenge of immune checkpoint inhibitors may be an option after explaining the risk of relapse of immune-related adverse events.

Keywords: Carcinoma, Renal Cell • Lung Diseases, Interstitial • Nivolumab

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932924

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Background

The CheckMate-025 trial demonstrated the significance of nivolumab over everolimus for the treatment of advanced renal cell carcinoma (RCC) previously treated with antiangiogenic agents. The response rate for nivolumab was 23%, and the median duration of response was 18.2 months, indicating good results, but 9.6% had to discontinue nivolumab due to immune-related adverse events (irAEs) [1]. In the case of serious irAEs, permanent discontinuation of the immune checkpoint inhibitors (ICIs) is required; otherwise, the same ICI is often re-administered after the irAE has resolved. As there are no randomized trials examining ICI re-administration and there are only a few retrospective reports, the safety and efficacy of ICI re-administration after discontinuation due to irAEs remain unclear. We report the case of a patient with metastatic RCC who had a second response to re-administration of nivolumab after discontinuation due to interstitial pneumonia.

Case Report

A 52-year-old man underwent laparoscopic radical left nephrectomy for a 6.5-cm left renal mass. The pathological results indicated clear cell RCC, Fuhrman grade 4, and pT1bN0M0. The patient had no predisposing factors for RCC. Five years later, a left adrenal metastasis appeared.

Since he did not wish to undergo adrenalectomy, he was treated with various targeted therapy agents (sorafenib, sunitinib, everolimus, axitinib, and pazopanib). However, lung metastases appeared, and the left adrenal metastasis developed 12 years after the surgery (**Figure 1A**). Nivolumab therapy was initiated as the sixth-line therapy.

Nivolumab (3 mg/kg) was administered every 2 weeks. After 3 cycles of administration, he presented with cough. Computed tomography (CT) revealed reticular interstitial shadows in both lungs on the right predominant side (**Figure 2A**). He was diagnosed with grade 2 interstitial pneumonia, and nivolumab therapy was discontinued. He was treated with steroidal pulse therapy, and the interstitial pneumonia improved quickly. After the pulse therapy, he was administered a down-titrated oral prednisolone dose. Steroid therapy was terminated after 14 months. At the time of diagnosis of interstitial pneumonia, both lung and adrenal metastases were reduced, as documented by CT. The patient achieved (**Figure 1B**) and maintained partial response (PR) after nivolumab discontinuation; lung metastases disappeared 7 months after discontinuation (**Figure 1C**). Ten months after nivolumab discontinuation, bilateral lung metastases reappeared, but the patient was not treated because of the risk of irAEs. After 23 months of nivolumab discontinuation, the lung metastases progressed, and his cough worsened (**Figure 3A**).

We decided to re-challenge with nivolumab and explained the risk of recurrence of interstitial pneumonia in the patient. After re-administration of nivolumab, the patient underwent a chest X-ray and had consultations with a respiratory physician every 2 weeks. The day after re-administration, he developed a grade 1 fever that subsided spontaneously without antibiotics. He continued nivolumab therapy without any other adverse events. After 5 cycles of re-administration, CT revealed a reduction in all metastases (**Figure 3B**), and the patient achieved PR again.

However, after 7 cycles of treatment, the lung metastases increased again, and nivolumab treatment was terminated (**Figure 3C**). Two months after nivolumab discontinuation, a chest X-ray revealed consolidation. Subsequent CT showed a recurrence of grade 2 interstitial pneumonia with a contralateral left predominance (**Figure 2B**). We administered down-titrated oral prednisolone (1 mg/kg) that rapidly improved the interstitial pneumonia. Nine months after nivolumab discontinuation, there was no further evidence of interstitial pneumonia, and the patient was placed under observation and provided with the best supportive care.

Discussion

In the CheckMate-025 study, interstitial pneumonia was observed in 5.2% of the patients, of which 71.4% had grades 1-2, 28.6% had grades 3-4, and none had grade 5 [1]. According to the guidelines, re-administration of ICIs after grade 2 irAEs is allowed if the patient has improved to grade 1 or lower, but re-administration is not recommended for patients with grade 3 or higher [2-4].

Recently, there have been retrospective reports of re-administration of ICIs for metastatic RCC. Abou Alaiwi et al analyzed 45 cases of metastatic RCC that were re-administered with ICIs after discontinuation due to irAEs and reported a response to ICI re-treatment in 23.1% of patients who did not respond to the initial ICI treatment [5]. IrAE recurrences were observed in 50% of cases, but no grade 4 and 5 irAEs were observed, and there was no correlation between the grades of the first irAE and the second irAE. Ravi et al reported 69 patients who received at least 2 separate lines of ICI for RCC [6]. PR was obtained in 37.5% of patients who were re-administered with other ICIs after discontinuation due to irAEs, which was higher than the 37% overall response rate of the initial ICI treatment. Patients who developed irAEs on the initial ICI treatment had a significantly higher risk of developing irAEs with ICI re-challenge than patients who did not (41% vs 20%). However, this rate was low compared to the 71% rate of developing irAEs with the initial ICI treatment. Grade 3 or higher irAEs were observed in 26% of patients treated with the initial ICI and in 16% of patients with ICI re-treatment.

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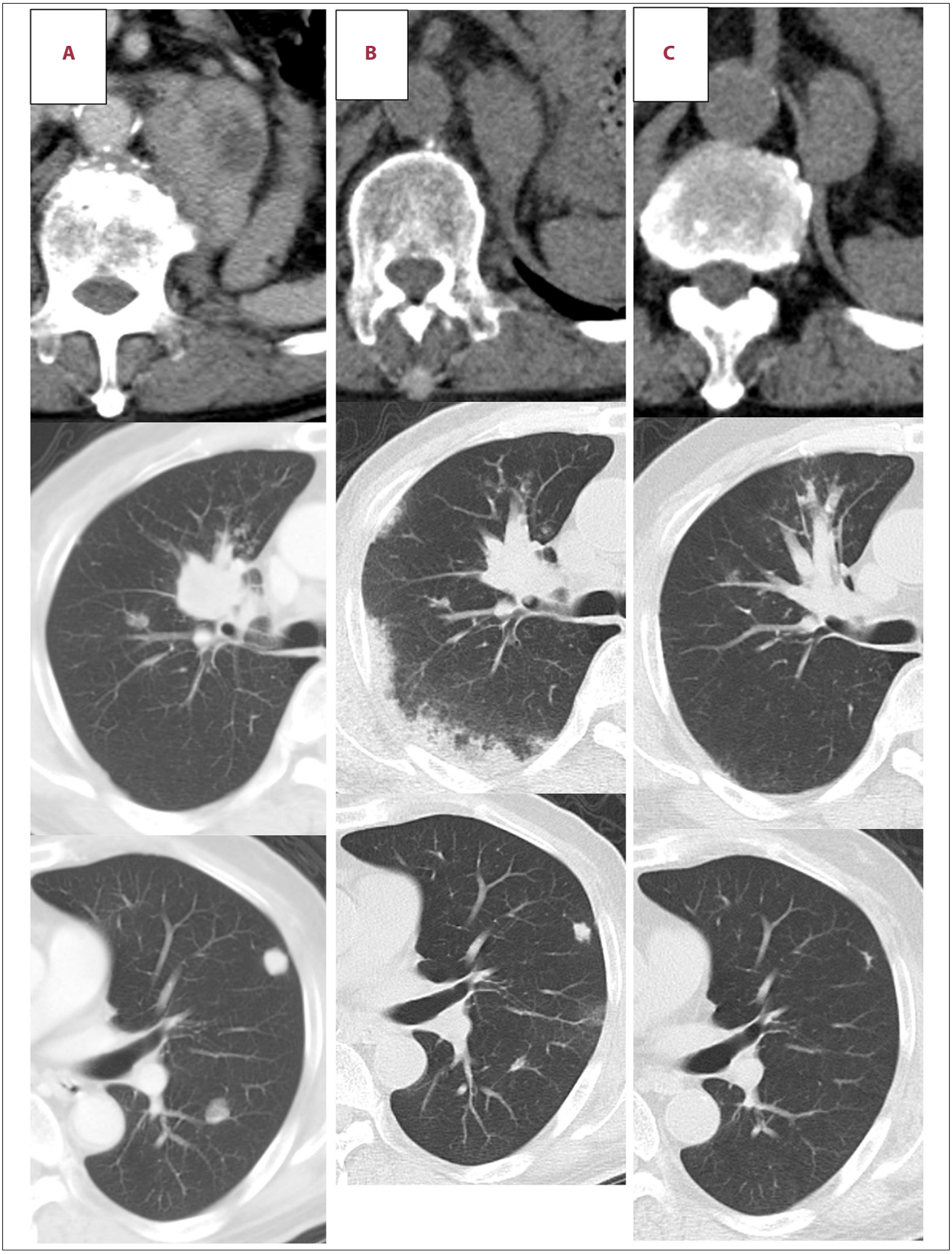

Figure 1. The CT scan shows left adrenal and lung metastases before initial nivolumab therapy (**A**), after 3 cycles of nivolumab therapy (**B**), and 7 months after nivolumab discontinuation (**C**).

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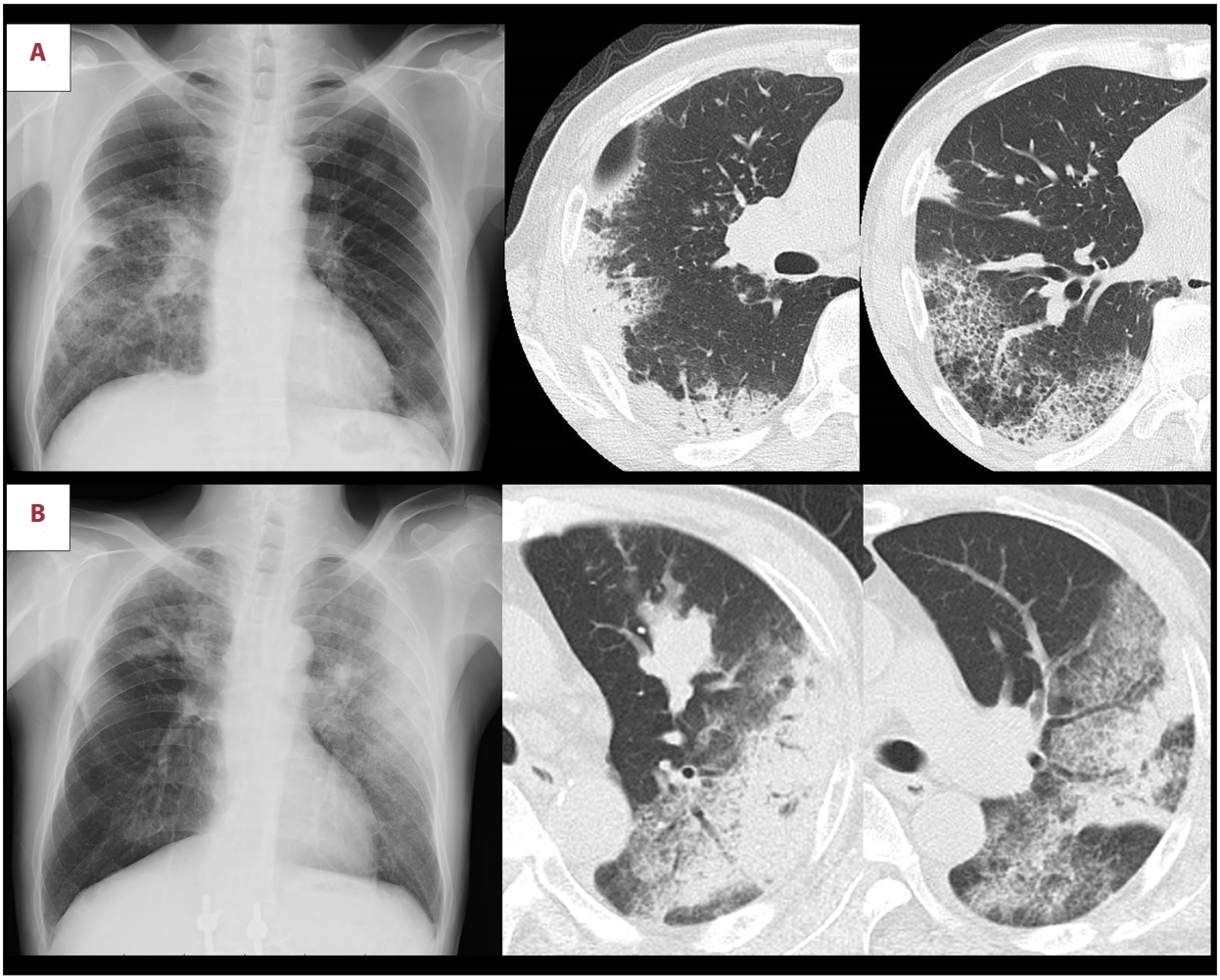

Figure 2. X-rays and CT when interstitial pneumonia appeared. (**A**) Interstitial pneumonia after 3 cycles of nivolumab treatment. (**B**) Recurrence of interstitial pneumonia after re-challenge with nivolumab.

The reasons for the low rate of irAEs after ICI re-administration include the possibility that irAE recurrence beyond the observation period may have been missed, and that the use of steroids or immunosuppressive agents during ICI re-administration may have affected irAE recurrence. In patients with melanoma, it has been reported that the recurrence rate of irAEs decreased after ICI re-treatment after anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monotherapy, and that the history of anti-CTLA-4 treatment did not affect the recurrence rate of a grade 3 or higher irAEs with anti-programmed cell death 1 antibodies re-treatment [7,8]. The mechanism of irAE recurrence is not yet understood, although differences in the mechanism of action of ICIs may contribute to a lower rate of irAE recurrence in the re-administration of different ICIs, as reported for melanoma by Ravi et al [6].

In other carcinomas, factors involved in the effect of ICI re-challenge and irAE recurrences have been reported. Santini reported that patients who did not respond to the initial ICI treatment before irAEs showed improvement in progression-free survival and overall survival after ICI re-challenge [9]. He further reported that the factors contributing to irAE recurrence were (1) initial irAEs requiring hospitalization and (2) PR or complete response after the first ICI administration. Simonaggio also reported a shorter time to onset of the first irAE in patients with irAE recurrence than those with no recurrence (9 vs 15 weeks; *P*=0.04) [10].

In this case, the patient had a durable response after interruption of ICI treatment but then progressed and was re-treated with the same ICI, resulting in another response. There are few reports on the efficacy of re-challenging with the same ICI when patients progress after a durable response, as in this case. Reports of durable response in other carcinomas showed that many cases progressed within 2 years, and about 20% of patients responded to the same ICI [11].

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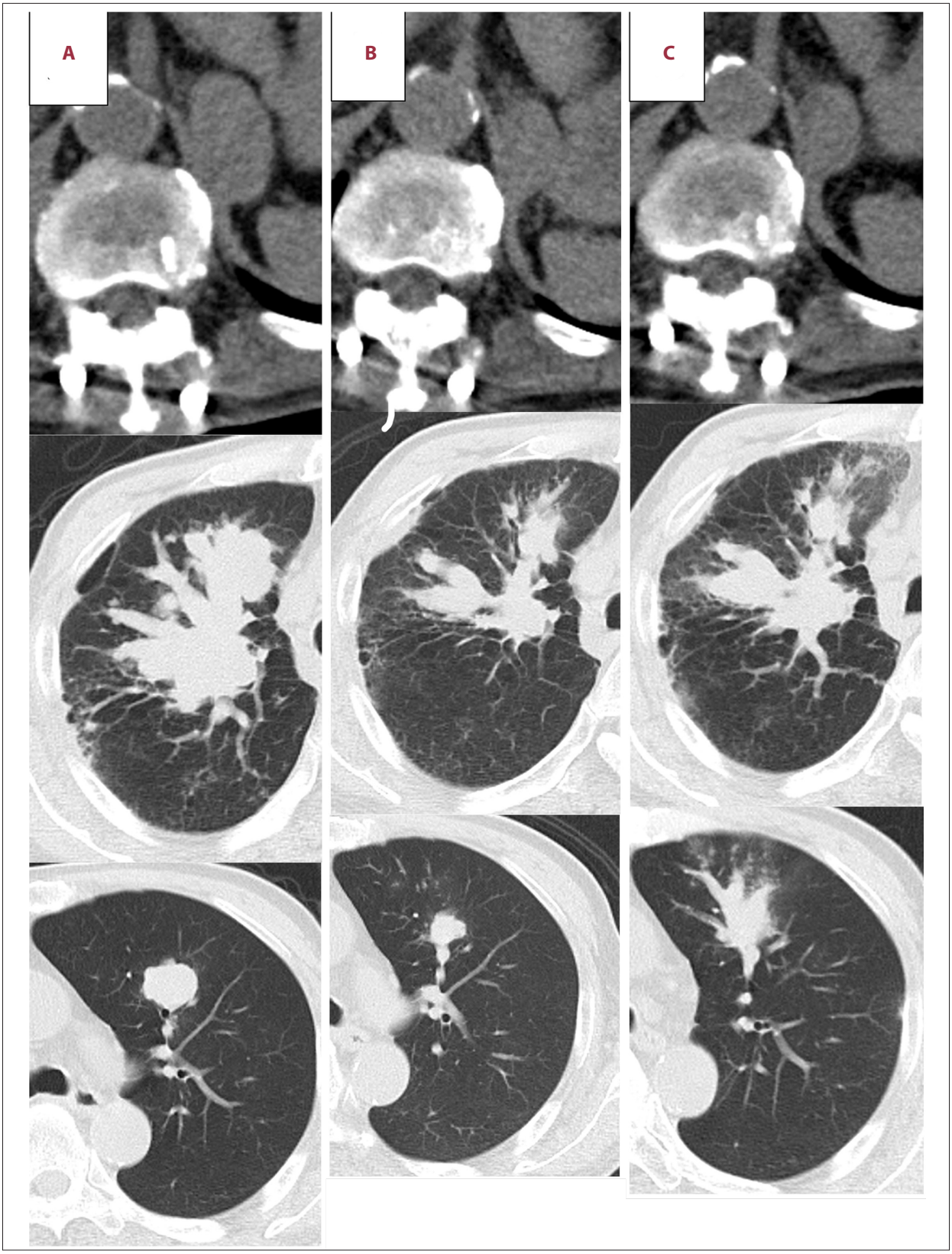

Figure 3. The CT scan shows left adrenal and lung metastases before re-challenge with nivolumab (**A**), PR after 5 cycles of re-administration (**B**), and enlarged after 7 cycles of re-administration (**C**).

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These data suggest that an additional response and overall survival prolongation may be achieved with ICI re-challenge. Although there was no significant worsening of the grade or incidence of irAEs with ICI re-treatment compared with the initial ICI treatment, caution is required because there is no established follow-up method for early detection of irAE recurrence and there are no randomized data on the safety and efficacy of ICI re-challenge.

Conclusions

ICI re-challenge after irAE can be an option after patients are fully informed of the risk of irAE relapse. It is important to re-challenge ICIs cautiously in collaboration with other specialists.

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Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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