Case Report

A case of sarcoidosis-like reaction associated with immune checkpoint inhibitors in metastatic renal cell carcinoma

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Abbreviations & Acronymns
ACE = angiotensin-converting enzyme
CT = computed tomography
DILI = drug-induced liver injury
ICI = immune checkpoint inhibitor
Ip-Nv = combination therapy with ipilimumab and nivolumab
irAE = immune-related adverse event
RCC = renal cell carcinoma
sIL2R = soluble interleukin 2 receptor
SLR = sarcoidosis-like reaction

Introduction: Immune checkpoint inhibitors are one of the standard treatments for metastatic renal cell carcinoma. Among immune-related adverse events, the sarcoidosis-like reaction is frequently difficult to differentiate from cancer progression.
Case presentation: A 58-year-old man with renal cell carcinoma with multiple lung metastases was treated with ipilimumab and nivolumab after nephrectomy. Computed tomography after three courses of treatment revealed hilar/mediastinal lymphadenopathies, pleural nodules, and pulmonary interstitial lesions, whereas lung metastases were markedly regressed. Considering positive findings of Gallium scintigraphy and serological tests together, we clinically judged the new lesions as a sarcoidosis-like reaction and continued the treatment until cessation by liver dysfunction. After discontinuation of the immunotherapy, the sarcoidosis-like reaction was regressed without cancer relapse.
Conclusion: We report here the first case of a clinically diagnosed sarcoidosis-like reaction in metastatic renal cell carcinoma following treatment with immune checkpoint inhibitors.

Key words: immune checkpoint inhibitor, immune-related adverse event, renal cell carcinoma, sarcoidosis-like reaction.

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How to cite this article: Katagiri A, Yamazaki H, Ikeda T. A case of sarcoidosis-like reaction associated with immune checkpoint inhibitors in metastatic renal cell carcinoma. *IJU Case Rep*. 2022; **5**: 15–18.

Received 27 May 2021; accepted 25 August 2021.
Online publication 24 September 2021

Keynote message

We should be aware of the possibility of sarcoidosis-like reaction as an immune-related adverse event in the treatment of immune checkpoint inhibitors for advanced cancer including renal cell carcinoma. Differential diagnosis from cancer progression is crucial for the subsequent strategy.

Introduction

Sarcoidosis is a systemic inflammatory granulomatous disease characterized by noncaseating granuloma in pathology. Various malignancies and related drugs have been reported to be associated with similar granulomatous lesions called SLRs.[1–4] We experienced a case of a clinically diagnosed SLR in metastatic RCC following treatment with ICIs.

Case presentation

A 58-year-old man was referred to our hospital with abnormal findings from a chest X-ray. He had a history of smoking for 35 years and was medicated for chronic gastritis and hypertension. CT revealed a left renal tumor with bilateral multiple lung metastases (Fig. 1a–c). First, left laparoscopic nephrectomy was performed, and the tumor was pathologically diagnosed as a clear cell subtype of RCC with Fuhrman grade 4. With good performance status and normal laboratory data, he was considered an intermediate risk in the criteria of International Metastatic RCC Database Consortium. Then the combination therapy with four courses of ipilimumab (1 mg/kg) and nivolumab (240 mg) of every 3 weeks followed by nivolumab (240 mg) of every 2 weeks was started. After two courses of Ip-Nv, skin lesions like lichen

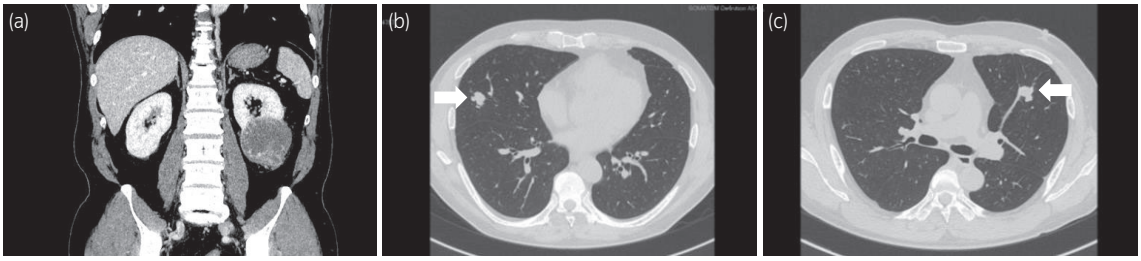

Fig.1 CT findings of the left renal tumor with lung metastases. (a) Left renal tumor and (b, c) multiple lung metastases (arrows).

striatus appeared on the face and neck. He did not accept biopsies. We considered the skin lesions as an irAE and treated them with corticosteroid ointment. The lesions were remitted in a month with residue of skin scleroses and were followed by additive medication of tranilast. On the CT after three courses of Ip-Nv, lung metastases were markedly regressed, whereas bilateral hilar/mediastinal lymphadenopathies, pleural nodules, and pulmonary interstitial micronodular lesions mimicking lymphangitic carcinomatosis were appeared without respiratory symptoms (Fig. 2a, b, c). Increased levels of ACE (25.1 U/L) and sIL2R (1337 U/mL), and accumulation at bilateral pulmonary hilar regions in Gallium scintigraphy suggested the possibility of sarcoidosis. We comprehensively diagnosed the new lesions as SLRs due to ICIs, although the histological diagnosis was not acquired. As there was no finding of other organ involvement, we continued the ICI treatment without definite medications for the SLR. After four courses of Ip-Nv and four courses of nivolumab, increased aminotransferases of grade 4 in Common Terminology Criteria for Adverse Events v5.0 appeared. The ICI treatment was discontinued while

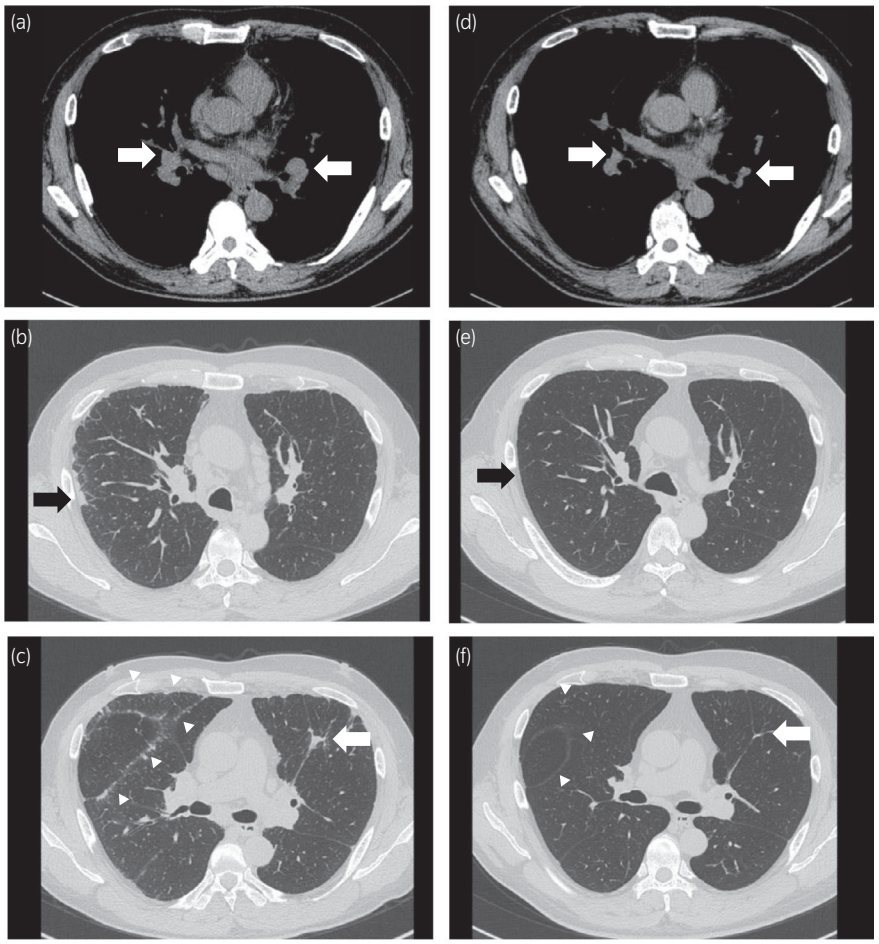

Fig. 2 CT findings after three courses of Ip-Nv (a, b, c) and 6 months after the last ICI treatment (d, e, f). (a, d) Bilateral hilar lymphadenopathies (arrows), (b, e) pleural nodules (arrows), (c, f) interlobular pleural lesions (arrowheads), and the metastatic lesion on Fig. 1c (arrows). (b, c) Diffuse interstitial micronodular lesions also appeared after three courses of Ip-Nv.

maintaining stable disease of the SLR and complete remission of the metastases. The liver dysfunction was stable but persisted for a week. Then liver biopsy revealed acute hepatocellular and biliary damage and various cell infiltration not dominated by plasma cells without definite interface hepatitis or granuloma, which were not typical findings for autoimmune hepatitis or sarcoidosis but were compatible with DILI. Antinuclear antibodies were not detected and viral hepatitis was denied. Considering the clinical course together, we diagnosed him with DILI due to tranilast, which was stopped thereafter, and the liver function normalized in weeks. After the withdrawal of ICIs, the SLR regressed gradually and remitted in 6 months without cancer relapse (Fig. 2d, e, f).

Discussion

ICIs are one of the main treatments for metastatic cancers including RCC. ICI treatment can lead to various complications termed irAEs.[1,2] Among irAEs, the frequency of SLRs is reported as 0.2–22%.[1–4] Various incidences might attribute to divergent drugs, fewer symptoms, and incorrect diagnosis as progression or pseudoprogression. Although the mechanism of sarcoidosis is not fully understood, ICI-induced SLR may be related to the modulation of T lymphocytes and antigens derived from destroyed cancer cells. In the review of Gkiozos et al., the onset of SLR after ICI initiation was 14 weeks in the median, and more cases were reported in melanoma.[3] ICIs responsible for SLR contain antiprogrammed cell death protein 1, antiprogrammed cell death ligand 1, and anticytotoxic T lymphocyte-associated protein 4 among which ipilimumab has been reported to accompany SLR more frequently in consistent with other irAEs.[2–4]

When SLR is suspected during the treatment of malignancy, differentiation from cancer progression is critical, which affects the decision-making of whether the treatment should be continued or not. Ravaglia et al. conducted transbronchial needle aspiration to differentially diagnose mediastinal hilar/mediastinal lymphadenopathies in patients of various cancers.[5] They reported nonnecrotizing granulomas suggestive of sarcoidosis in 12 (26.7%), lymph node metastases in 13 (28.9%), and hyperplastic nonspecific lymphadenopathy in 20 (44.4%) among 45 samples. In general, histological detection is recommended for differentiation because of the poor specificity of SLR in imaging. The present case showed multiple new lesions radiographically compatible with SLR, which also resembled lymphangitic carcinomatosis. Lymphangitic carcinomatosis is rare in RCC and is usually accompanied by respiratory symptoms which were not seen in this case.[6] In contrast to the new lesions, lung metastases regressed to complete remission. Although not specific strictly, increased levels of ACE and sIL2R were also compatible with sarcoidosis.[2,7] As is the common case with SLR, this case exhibited a clinical course similar to pseudoprogression which is defined as regression after initial progression including new lesions and is occasionally observed in immunotherapy. In this case, there might be the possibilities of other inflammatory reaction, pseudoprogression, and mixed response; the appearance of new metastatic lesions with regression of the original metastases. Although they could not be completely excluded without biopsy, clinical findings suggestive of SLR and no symptomatic deterioration prompted us to pursue the immunotherapy. As for the skin lesions in this case, for lack of histological confirmation, we could not differentiate between other irAEs and sarcoidosis in which skin lesion is common secondary to lung lesion. To the best of our knowledge, this is the first reported case of SRL clinically diagnosed in metastatic RCC following ICI treatment.

Treatment of SLR basically conforms to that of systemic sarcoidosis. In most cases of ICI treatment, SLR was reported to be improved after discontinuation of ICI and/or corticosteroid therapy.[1,2] As is in this case, only follow-up without cessation of responsible drugs is also considered if there is no symptom or involvement of organs including the central nervous system, eye, heart, etc. Chorti et al. reported seven cases of ICI-induced SLR including two radiographically diagnosed cases, among which SLR was remitted or resolved in six and stable in one although ICI treatment was continued after diagnosis of SLR.[4] Regarding prognosis and ICI treatment, association with irAEs have been reported to contribute to better outcome.[3,4] In previous reports, the prognosis of patients with SLR in ICI treatment seems to have been favorable or comparable with that of a general cohort.[3,4] In the present case, complete remission was attained with the appearance of SLR and was maintained even after cessation of ICI treatment.

Conclusion

Currently, ICIs are popularly used in the treatment of advanced RCC. We should be aware of the possibility of SLR as an irAE. In the suspected case of SLR following ICIs, differential diagnosis from cancer progression is crucial for the subsequent strategy. A biopsy is generally recommended at present, as radiological and serological findings are not definitive.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed Consent

Written informed consent for publication from the patient and institutional review board approval was obtained (approval number 2113).

Registry and the registration no. of the study/trial

Not applicable.

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Editorial Comment

Editorial Comment to A case of sarcoidosis-like reaction associated with immune checkpoint inhibitors in metastatic renal cell carcinoma

Immune checkpoint inhibitors, which have become a mainstay of treatment for advanced renal cell carcinoma, are associated with immune-related adverse events (irAEs). The mechanisms involved in the development of irAEs are incompletely understood, however, the most frequent mechanism of irAEs involves the aberrant activation of T cells targeting healthy tissue. Sarcoidosis-like reaction (SLR) is one of the rare irAEs. SLR involves systemic inflammation characterized by granuloma formation. SLR most commonly occurs in the lung, skin, and lymph nodes, but it can also affect the eyes, heart, nerves, and other organs.

In this issue of *IJU Case Reports*, Katagiri et al.[1] reported the case of this rare irAE in metastatic renal cell carcinoma patients who received nivolumab and ipilimumab. Although a pathological confirmation could not be obtained, they clinically diagnose SLR based on serum marker levels (ACE and sIL2R) and imaging study (gallium scintigraphy). After the withdrawal of immunotherapy, SLR regressed without disease progression. Their case suggested that immune-related SLR did not require intensive therapy, except for the interruption of immunotherapy.

The differential diagnosis of SLR from cancer progression is crucial for optimal management, however, SLR may mimic metastases and neither imaging nor serum marker could not differentiate it from metastases. Biopsy of affected sites is crucial and should be considered whenever possible, as discussed by the authors. Urologists who prescribe checkpoint inhibitors need to be aware of this rare irAE because cases previously diagnosed as progression or pseudoprogression could have been with SLR.

In this case, SLR regressed without tumor progression after withdrawal of checkpoint inhibitors. The possible association between the development of irAEs and efficacy of checkpoint inhibitors has been widely reported.[2] As for immune-related SLR, Chorti et al.[3] reported that there was no difference in recurrence rates between melanoma patients with SLR (2/10, 20%) and those without SLR (7/35, 20%). Further accumulation of cases with immune related SLR is warranted to evaluate the association of SLR and efficacy of immunotherapy.

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DOI: 10.1002/iju5.12393

Conflict of interest

The authors declare no conflict of interest.

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