Received: 14 March 2022 | Revised: 19 May 2022 | Accepted: 30 May 2022

DOI: 10.1002/ccr3.5960

CASE REPORT

Clinical Case Reports Open Access WILEY

Suspected immune checkpoint inhibitor-induced pulmonary sarcoid reaction in metastatic renal cell carcinoma

Victoria Purcell[1] | **Beatrice Preti**[1,2] | **Ricardo Fernandes**[1,2,3]

[1]Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[2]Division of Medical Oncology, Department of Oncology, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

[3]Cancer Research Laboratory Program, Lawson Health Research Institute, London, Ontario, Canada

Correspondence
Ricardo Fernandes, Department of Oncology, London Health Sciences Centre, Western University, 800 Commissioners Road East, Room A3-940, London, Ontario N6A 5W9, Canada.
Email: ricardo.fernandes@lhsc.on.ca

Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Abstract

We present the case of a 50-year-old male patient with metastatic clear cell renal cell carcinoma (mRCC) who developed a diffuse pulmonary opacification and lymphadenopathy during nivolumab maintenance therapy. This was diagnosed as presumed sarcoid granulomatous inflammatory reaction secondary to immunotherapy, which resolved with holding off therapy and the nivolumab was resumed.

KEYWORDS

immune-related adverse events, immunotherapy, metastatic renal cell carcinoma, sarcoid-like reactions

1 | INTRODUCTION

The advent of immunotherapy with immune checkpoint inhibitors (ICI) has revolutionized the treatment landscape in oncology. These drugs administered as single agent or in combination have dramatically improved patient survival and are highly effective at inducing response and disease control.[1] Anti-cytotoxic T lymphocyte antigen 4 (CTLA4) (ipilimumab) and anti-programmed death 1 (PD-1) (nivolumab) monoclonal antibodies enhance antitumor immunity in the treatment of metastatic renal cell carcinoma (mRCC) and melanoma, among other solid cancers.[2] Despite clinical efficacy, immune checkpoint blockades can result in off-target immune activation leading to undesirable immune-related adverse events (irAEs), such as colitis, hepatitis, and rash.[3] Most irAEs tend to be mild and self-limiting, but in few severe cases (grade 3 or 4) potentially life-threatening events can occur requiring multidisciplinary management, intensive care, and treatment discontinuation.[4]

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

A sarcoid reaction is a rare irAE, with only two other cases reported in the treatment of mRCC with immunotherapy.[5] These reactions are characterized by the development of non-caseating granulomas in the affected organ, most commonly the lungs. While the previously documented cases presented as skin lesions or lymphadenopathy, our case demonstrates the reaction can radiographically present as pulmonary micronodules and lymphadenopathy together, potentially leading to misdiagnosis of true disease progression. We report below a presumed sarcoid granulomatous inflammatory reaction that phenotypically resembled metastatic disease following treatment of mRCC with combined ipilimumab and nivolumab, highlighting the importance of accurate identification and management of sarcoid reactions.

2 | CASE PRESENTATION

A 50-year-old male patient presented to the emergency department in May 2018 with acute intermittent right-sided flank pain, associated with urinary retention and gross hematuria. Contrast-enhanced computed tomography (CT) scans confirmed an irregular mass measuring 12×8 cm in the right kidney and borderline lymphadenopathy in the inter-aortocaval region. The heterogenous enhancement and peripheral calcification of the mass on CT was suspicious for malignancy, and a referral to urology was arranged. The patient's past medical history was unremarkable, aside from well-controlled hypertension. The patient denied any history of autoimmune disease. At the time of presentation, he was an active smoker with a 20 pack-year smoking history.

One week later, a renal biopsy was carried out. The results were consistent with clear cell RCC, and a right radical nephrectomy was performed. Pathological examination confirmed clear cell RCC, Fuhrman grade 3, 30% tumor necrosis, and LVI-positive with positive surgical margins. No sarcomatoid or rhabdoid features were identified, and no lymph nodes were submitted. Final pathologic staging was T3Nx. Adjuvant therapy was not pursued, and active surveillance was recommended.

Six months post-operatively, surveillance CT scans revealed multiple new bilateral pulmonary nodules with the largest measuring 11 mm. In addition, there were several prominent mediastinal and bilateral hilar lymph nodes measuring up to 9 mm in short axis in a right paratracheal location, as well as several portacaval and porta hepatis lymph nodes measuring up to 1.4 cm in size. The case was reviewed and discussed in our tumor board, and a pulmonary biopsy or wedge resection was not feasible at this time due to the location of the nodules. This was clinically determined to be recurrent, metastatic RCC based on the RCC pathology and the short interval between surgery and the development of findings consistent with metastatic disease on imaging. The RCC disease was categorized as intermediate prognostic risk disease based on the International Metastatic Renal Cell Carcinoma Database (IMDC) Criteria. The patient was consented to a trial of nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab maintenance therapy 3 mg/kg every 2 weeks.

The treatment was initially well-tolerated, aside from the development of immunotherapy-related hypothyroidism and myositis following the fourth cycle of immunotherapy combination. The patient's T3 and T4 levels were <1.5 and <2, respectively, with TSH levels within normal limits. The patient's CK levels elevated from 78 to 573 U/L, and the treatment was held. He was prescribed levothyroxine 125 mcg for thyroid supplementation, and the myositis responded well to corticosteroid treatment with improvement of the symptoms and CK laboratory levels.

At this time, the patient's 3-month imaging for restaging purposes revealed interval enlargement of several lymph nodes and the development of innumerable pulmonary nodules suspicious for metastatic disease. After discussion at the multidisciplinary tumor board, it was felt that this was likely pseudo-progression since the patient was clinically asymptomatic. The tumor board recommended the initiation of nivolumab maintenance

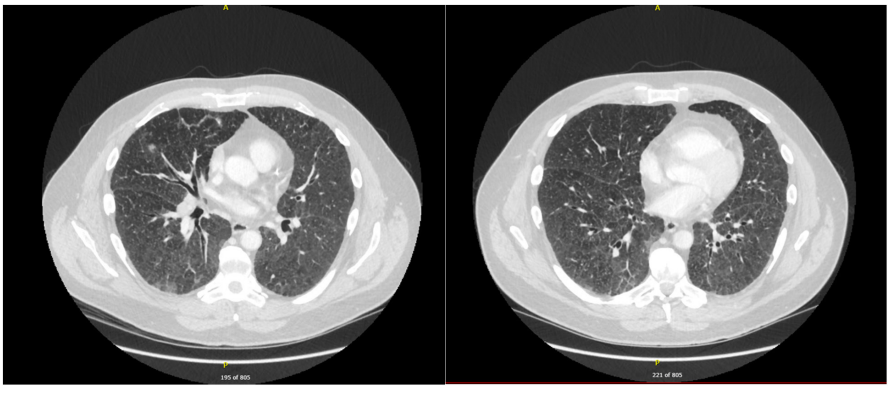

FIGURE 1 Imaging characteristics of the initial pulmonary abnormality presentation on computed tomography (CT) of the chest

therapy and short interval CT scans in 8 weeks. Repeat imaging revealed interval decrease in the size of multiple mildly enlarged upper abdominal lymph nodes and interval improvement in the previously identified pulmonary nodules, favoring partial response to treatment based on RECIST 1.1 criteria.

Maintenance therapy was continued, and the disease remained stable. Following the fifth cycle of nivolumab, the patient presented with dry eyes and blurry vision, which was clinically diagnosed by ophthalmology as bilateral acute uveitis secondary to immunotherapy. Nivolumab was held once again, and the uveitis responded well to an ophthalmic suspension of prednisolone.

The plan was to reinitiate nivolumab after being off therapy for 6 weeks; however, imaging at this time revealed a diffuse micronodular pulmonary abnormality (Figure 1). This was characterized by sub-miliary sized tiny nodules with mosaic attenuation most prominent at the lung apices and a minor degree of ground-glass density at the lung bases. In addition, there was a reduction in volume of upper abdominal lymphadenopathy with stable thoracic lymph nodes. Concern was raised for hematological dissemination of the neoplasm to the pulmonary capillary level or an infectious disease. The patient was clinically stable with normal oximetry and did not have any respiratory distress. The patient was therefore referred to respirology.

The patient was asymptomatic, apart from a slight dry cough, and his pulmonary function test was normal. He denied any known infectious exposures. Given this information, the decision was made to not treat the patient with corticosteroids. In discussion with respirology, the temporal relationship between immunotherapy and the development of the lung findings raised the possibility of a treatment-related side effect. A bronchoscopy with transbronchial biopsy was considered and presented to the patient, who refused the procedure. The mediastinal lymph nodes themselves were felt to be fairly small to yield for endobronchial ultrasound and biopsy. Upon discussion with the patient, Nivolumab was resumed as the disease was otherwise responding well to treatment.

Two months after resuming nivolumab, repeat imaging demonstrated marked clearing of the diffuse opacity and pulmonary nodules, as well as interval improvement of the intrathoracic lymphadenopathy (Figure 2). Given the consistent radiological findings and clinical presentation, the patient was diagnosed with a presumed sarcoid granulomatous inflammatory reaction secondary to the immunotherapy.

Nivolumab was permanently discontinued approximately 1 year later due to recurring grade 3 colitis, biopsy-proven to be immunotherapy-related. At 3 years post-diagnosis, the patient's disease remains stable. With the patient's demonstrated level of immune response and data supporting an intimate association between autoimmunity with the irAEs and antitumor effect of checkpoint inhibitors,[6] it is hoped that the disease will remain dormant long-term.

3 | DISCUSSION

The novel immunotherapeutics with ICI have dramatically improved survival of cancer patients and are highly effective at inducing response and disease control. In patients with mRCC, combination immunotherapy with anti-CTLA-4 and anti-PD-1 demonstrated significantly better progression-free survival, overall survival, and response rates when compared to tyrosine kinase inhibitor (TKI) monotherapy.[7] As this efficacy relies on blocking immune-regulators, adverse events due to aberrant immune responses are an inherent part of therapy, with dermatologic and endocrine reactions among the most common.[3] Sarcoid reactions, however, have only been reported in 5% and <0.5% of patients treated with anti-CTLA-4 and anti-PD-1/PD-L1 regimens, respectively.[2] Table 1 presents a summary of ICI-induced sarcoid-like reactions reported in the literature.

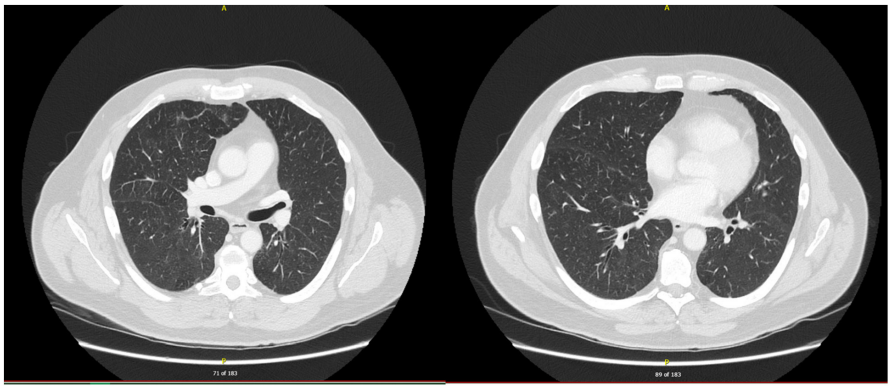

FIGURE 2 Resolution of the pulmonary abnormality on computed tomography (CT) of the chest 2 months later

TABLE 1 Overview of ICI-induced sarcoid-like reactions reported in the literature

Reported ICI-induced sarcoid-like reactions ($N = 103$)[a]	
ICI	Ipilimumab (26, 25); nivolumab (19, 18); combination ipilimumab and nivolumab (23, 22); pembrolizumab (30, 29); atezolizumab (1, 1); durvalumab (1, 1); unspecified anti-PD-1 (3, 3)
Malignancy	Melanoma (83, 81); uterine sarcoma (1, 1); urothelial Ca (2, 2); metastatic ovarian Ca (1, 1); metastatic RCC (2, 2); metastatic esophageal (1, 1); small cell lung cancer (1, 1); NSCLC (6, 6); gallbladder adenoCa (1, 1); lymphoma (2, 2); metastatic lung cancer (1, 1); prostate cancer (1)
Site of SLR[b]	Lung parenchyma (30, 29); cutaneous (44, 42); hilar lymph nodes (64, 62); mediastinal lymph nodes (66, 64); bone (5, 5); neural tissue (3, 3); kidney (1, 1); extrathoracic lymph nodes (5,5); spleen (4, 4); eye (5,5)

Abbreviations: adenoCa, adenocarcinoma; Ca, carcinoma; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma, SLR, sarcoid-like reaction.

[a]Multiple organs could be involved per case. The total sites involved are greater than number of reactions (N).

[b]Based on reports found in the reference list [5,10–80].

We reported the second case of a presumed immunotherapy-induced sarcoid granulomatous inflammatory reaction in the treatment of mRCC. Sarcoid reactions typically present as non-caseating granulomatous inflammation, with the clinical manifestations depending on the organ involved. This is commonly the lungs and/or the skin, where they can be identified as pulmonary micronodules or cutaneous lesions, respectively. The majority of these reactions tend to be asymptomatic and resolve without discontinuing the offending drug or administering corticosteroids. It is imperative that immunosuppressive treatment is only used when warranted, as it often necessitates the discontinuation of immunotherapy.[2]

The pathogenesis of immunotherapy-induced sarcoid reactions is not yet fully understood. It is posited that a strong autoimmune response results from regulatory T (Treg) cell impairment, T-helper 1 (Th1) and 17 (Th17) cell activation, and inflammatory cytokine stimulation. Specifically, CTLA-4 blockade with ipilimumab is associated with increased proportions of Th1 and Th17 cells, which are abundant in active sarcoidosis and play an integral role in the formation of sarcoid granulomas. Additionally, the peripheral blood and bronchoalveolar lavage samples of sarcoidosis patients showed increased Th17/Treg ratios similar to the proportions seen with anti-CTLA-4 therapy.[8]

Interestingly, upregulation of PD-1 in sarcoid granulomas has been reported, and in vitro PD-1 blockades result in cellular patterns seen in the resolution of sarcoidosis.[2] Thus, anti-PD-1-induced sarcoidosis appears to be a paradoxical event, and further research is required to understand the role that immunotherapy plays in these reactions.

Sarcoid reactions have been primarily reported in the treatment of melanoma with ipilimumab monotherapy. They have rarely been documented in the use of nivolumab, and only one case has been described in the treatment of mRCC.[5,80] The main toxicities associated with ipilimumab and nivolumab combination occur during the 4 cycles of ipilimumab treatment since this anti-CTLA4-blocking drug can activate T cells early on inducing immune reactivity to targets outside the tumor.[9,10] However, some toxicities may occur with a delayed onset. Therefore, it would be hard to know which checkpoint inhibitor is associated with the presented case. The identification of this rare reaction is imperative as confounding it with malignancy dissemination can result in the unnecessary cessation of treatment. Multidisciplinary consultation and discussion play a particularly important role as the radiographic signs are nearly indistinguishable between this reaction and disease progression, presenting a therapeutic dilemma. Although biopsy with histologic confirmation remains the gold standard for diagnosis, it is not always feasible, as in the presented case. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Clinicians must consult with the appropriate service when warranted and be aware of the clinical clues, such as the temporal relationship to the immunotherapy.

This case underscores the importance of considering this diagnosis in all patients treated with immunotherapy who present with pulmonary micronodules and lymphadenopathy on imaging. Clinicians should be aware of these radiographic manifestations that may mimic metastasis and disease progression, and keep a broad differential to prevent interruptions to treatment. Furthermore, clinicians should be cognizant of the guidelines for managing irAEs as corticosteroids are not always warranted.[81] Fortunately, in this case, the immunotherapy was continued without progression of the sarcoidosis or clinical deterioration.

AUTHOR CONTRIBUTIONS

All authors involved in conception and design; manuscript writing; and final approval of manuscript.

ACKNOWLEDGEMENT

We thank the patient in this report. He hopes it will improve the experience of other patients.

CONFLICT OF INTEREST

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Ricardo Fernandes has following disclosures: Advisory Board or Honoraria: Merck, Novartis, Janssen, Pfizer, BMS, Ipsen, Bayer; Travel Grant: Janssen. The other authors have no other conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

ETHICAL APPROVAL

This manuscript is exempt from ethical committee approval, as per institutional policy, but complies with ethical guidelines set out by the Western Research Ethics Board, at Western University, London, ON, Canada.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Ricardo Fernandes https://orcid.org/0000-0002-7195-8246

REFERENCES

1. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharmacol*. 2018;62:29-39. doi:10.1016/j.intimp.2018.06.001
2. Gkiozos I, Kopitopoulou A, Kalkanis A, Vamvakaris IN, Judson MA, Syrigos KN. Sarcoidosis-like reactions induced by checkpoint Inhibitors. *J Thorac Oncol*. 2018;13(8):1076-1082. doi:10.1016/j.jtho.2018.04.031
3. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PloS One*. 2016;11(7):e0160221. doi:10.1371/journal.pone.0160221
4. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168. doi:10.1056/nejmra1703481
5. Zhang M, Schembri G. Nivolumab-induced development of pulmonary sarcoidosis in renal cell carcinoma. *Clin Nucl Med*. 2017;42(9):728-729. doi:10.1097/RLU.0000000000001758
6. Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors – A systematic review and meta-analysis. *Cancer Treat Rev*. 2021;92:102134. doi:10.1016/j.ctrv.2020.102134
7. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290.
8. Huang H, Lu Z, Jiang C, Liu J, Wang Y, Xu Z. Imbalance between Th17 and regulatory T-cells in sarcoidosis. *Int J Mol Sci*. 2013;14:21463-21473. doi:10.3390/ijms141121463
9. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined Nivolumab and Ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377:1345-1356. doi:10.1056/nejmoa1709684
10. Oh DY, Cham J, Zhang L, et al. Immune toxicities elicted by CTLA-4 blockade in cancer patients are associated with early diversification of the T-cell repertoire. *Cancer Res*. 2017;77:1322-1330. doi:10.1158/0008-5472.CAN-16-2324
11. Andersen R, Nørgaard P, Al-Jailawi MKM, Svane IM. Late development of splenic sarcoidosis-like lesions in a patient with metastatic melanoma and long-lasting clinical response to ipilimumab. *Onco Targets Ther*. 2014;3:e954506. doi:10.4161/21624011.2014.954506
12. Arellano K, Mosley JC, Moore DC. Case report of Ipilimumab-induced diffuse, nonnecrotizing granulomatous lymphadenitis and granulomatous Vasculitis. *J Pharm Pract*. 2018;31:227-229. doi:10.1177/0897190017699762
13. Berthod G, Lazor R, Letovanec I, et al. Pulmonary sarcoid-like granulomatosis induced by ipilimumab. *J Clin Oncol*. 2012;30:e156-e159. doi:10.1200/JCO.2011.39.3298
14. Birnbaum MR, Ma MW, Fleisig S, et al. Nivolumab-related cutaneous sarcoidosis in a patient with lung adenocarcinoma. *JAAD Case Rep*. 2017;3:208-211. doi:10.1016/j.jdcr.2017.02.015
15. Bronstein Y, Ng CS, Hwu P, Hwu WJ. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *Am J Roentgenol*. 2011;197:W992-W1000. doi:10.2214/AJR.10.6198
16. Burillo-Martinez S, Morales-Raya C, Prieto-Barrios M, Rodriguez-Peralto JL, Ortiz-Romero PL. Pembrolizumab-induced extensive panniculitis and nevus regression: two novel cutaneous manifestations of the post-immunotherapy granulomatous reactions spectrum. JAMA. *Dermatology*. 2017;153:721-722.
17. Cervantes J, Rosen A, Dehesa L, Dickinson G, Alonso-Llamazares J. Granulomatous reaction in a patient with metastatic melanoma treated with Ipilimumab: first case reported with isolated cutaneous findings. *Actas Dermosifiliogr*. 2019;110:43-49. doi:10.1016/j.ad.2017.11.021
18. Chahin M, Stack A, Siddiqi A, Shaikh M. Is it metastatic melanoma or is it sarcoidosis? Non-caseating granulomas due to pembrolizumab. *BMJ Case Rep*. 2020;13:e240701. doi:10.1136/bcr-2020-240701
19. Cheshire SC, Board RE, Lewis AR, Gudur LD, Dobson MJ. Pembrolizumab-induced sarcoid-like reactions during treatment of metastatic melanoma. *Radiology*. 2018;289:564-567. doi:10.1148/radiol.2018180572
20. Chiang J, Hebroni F, Bedayat A, Pourzand L. Case 286: Sarcoid like granulomatosis and lymphadenopathy—Thoracic

manifestations of Nivolumab drug toxicity. *Radiology*. 2021;298:471-475. doi:10.1148/radiol.2021191247
21. Choi ME, Lee KH, Won CH, et al. A case of erythema nodosum-like panniculitis induced by nivolumab in a patient with oesophageal cancer. *Australas J Dermatol*. 2019;60:154-156. doi:10.1111/ajd.12970
22. Chorti E, Kanaki T, Zimmer L, et al. Drug-induced sarcoidosis-like reaction in adjuvant immunotherapy: increased rate and mimicker of metastasis. *Eur J Cancer*. 2020;131:18-26. doi:10.1016/j.ejca.2020.02.024
23. Cotliar J, Raja N, Raz D, Boswell WJ, Chen R, Querfeld C. Pembrolizumab-associated sarcoidosis. *JAAD Case Rep*. 2016;2:290-293. doi:10.1016/j.jdcr.2016.06.004
24. Cousin S, Toulmonde M, Kind M, et al. Pulmonary sarcoidosis induced by the anti-PD1 monoclonal antibody pembrolizumab. *Ann Oncol*. 2016;27:1178-1179. doi:10.1093/annonc/mdw125
25. Danlos FX, Pagès C, Baroudjian B, et al. Nivolumab-induced sarcoid-like granulomatous reaction in a patient with advanced melanoma. *Chest*. 2016;149:e133-e136. doi:10.1016/j.chest.2015.10.082
26. Dimitriou F, Frauchiger AL, Urosevic-Maiwald M, et al. Sarcoid-like reactions in patients receiving modern melanoma treatment. *Melanoma Res*. 2018;28:230-236. doi:10.1097/CMR.0000000000000437
27. Dunn-Pirio AM, Shah S, Eckstein C. Neurosarcoidosis following immune checkpoint inhibition. *Case Rep Oncol*. 2018;11:521-526. doi:10.1159/000491599
28. Eckert A, Schoeffler A, Dalle S, Phan A, Kiakouama L, Thomas L. Anti-CTLA4 monoclonal antibody induced sarcoidosis in a metastatic melanoma patient. *Dermatology*. 2008;218:69-70. doi:10.1159/000161122
29. Fakhri G, Akel R, Salem Z, Tawil A, Tfayli A. Pulmonary sarcoidosis activation following neoadjuvant pembrolizumab plus chemotherapy combination therapy in a patient with non-small cell lung cancer: a case report. *Case Rep Oncol*. 2017;10:1070-1075. doi:10.1159/000484596
30. Firwana B, Ravilla R, Raval M, Hutchins L, Mahmoud F. Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. *J Oncol Pharm Pract*. 2017;23:620-624. doi:10.1177/1078155216667635
31. Fukuchi K, Hikawa M, Sano Y, et al. Sarcoid-like reaction and vitiligo occurring after nivolumab therapy in a patient with metastatic melanoma. *J Dermatol*. 2019;46:e359-e360. doi:10.1111/1346-8138.14887
32. Garanzini EM, Scaramuzza D, Spadarella G, Di Guardo L, Marchianò A. Sarcoidosis-like disease mimicking metastases during adjuvant ipilimumab therapy in advanced melanoma patient: CT scan and MRI help in managing difficult clinical decision. *BJR Case Rep*. 2020;6:20190065. doi:10.1259/bjrcr.20190065
33. Gilardi L, Colandrea M, Vassallo S, Travaini LL, Paganelli G. Ipilimumab-induced immunomediated adverse events: possible pitfalls in (18)F-FDG PET/CT interpretation. *Clin Nucl Med*. 2014;39:472-474. doi:10.1097/RLU.0b013e31828da691
34. González-Cruz C, Bodet D, Muñoz-Couselo E, Garciá-Patos V. Mediastinal FDG-positive lymph nodes simulating melanoma progression: drug-induced sarcoidosis like/lymphadenopathy related to ipilimumab. *BMJ Case Rep*. 2021;14:e237310. doi:10.1136/bcr-2020-237310
35. Jespersen H, Bjursten S, Ny L, Levin M. Checkpoint inhibitor-induced sarcoid reaction mimicking bone metastases. *Lancet Oncol*. 2018;19:e327. doi:10.1016/S1470-2045(18)30252-3
36. Keukeleire SD, Schwarze J, Awada G, et al. An atypical sarcoid-like reaction during anti-protein death 1 treatment in a patient with metastatic melanoma. *Melanoma Res*. 2020;30:524-527. doi:10.1097/CMR.0000000000000680
37. Kim C, Gao J, Shannon VR, Siefker-Radtke A. Systemic sarcoidosis first manifesting in a tattoo in the setting of immune checkpoint inhibition. *BMJ Case Rep*. 2016;2016:bcr2016216217. doi:10.1136/bcr-2016-216217
38. Koelzer VH, Rothschild SI, Zihler D, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. *J Immunother Cancer*. 2016;4:13. doi:10.1186/s40425-016-0117-1
39. Lainez S, Tissot C, Cottier M, Vergnon JM. EBUS-TBNA can distinguish sarcoid-like side effect of Nivolumab treatment from tumor progression in non-small cell lung cancer. *Respiration*. 2017;94:518-521. doi:10.1159/000480155
40. Laroche A, Chinchilla EA, Bourgeault E, Doré MA. Erythema nodosum as the initial presentation of nivolumab-induced sarcoidosis-like reaction. *J Cutan Med Surg*. 2018;22:627-629. doi:10.1177/1203475418776934
41. Le Burel S, Champiat S, Mateus C, et al. Prevalence of immune-related systemic adverse events in patients treated with anti-programmed cell death 1/anti-programmed cell death-ligand 1 agents: a single-Centre pharmacovigilance database analysis. *Eur J Cancer*. 2017;82:34-44. doi:10.1016/j.ejca.2017.05.032
42. Lidar M, Giat E, Garelick D, et al. Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. *Autoimmun Rev*. 2018;17:284-289. doi:10.1016/j.autrev.2018.01.003
43. Lise QK, Audrey AG. Multifocal choroiditis as the first sign of systemic sarcoidosis associated with pembrolizumab. *Am J Ophthalmol Case Rep*. 2017;5:92-93. doi:10.1016/j.ajoc.2016.12.014
44. Lomax AJ, McGuire HM, McNeil C, et al. Immunotherapy-induced sarcoidosis in patients with melanoma treated with PD-1 checkpoint inhibitors: case series and immunophenotypic analysis. *Int J Rheum Dis*. 2017;20:1277-1285. doi:10.1111/1756-185X.13076
45. Lu Y. FDG PET/CT course of Pembrolizumab-associated multiorgan sarcoidosis. *Clin Nucl Med*. 2019;44:167-168. doi:10.1097/RLU.0000000000002408
46. Luke JJ, Lezcano C, Hodi FS, Murphy GF. Antitumor granuloma formation by CD4+ T cells in a patient with rapidly progressive melanoma experiencing spiking fevers, neuropathy, and other immune-related toxicity after treatment with ipilimumab. *J Clin Oncol*. 2015;33:e32-e35. doi:10.1200/JCO.2013.49.7735
47. Marcoval J, Bauer-Alonso A, Fornons-Servent R, Jiménez-Colomo L, Sabaté-Llobera A, Penín RM. Subcutaneous sarcoidosis induced by pembrolizumab in a melanoma patient mimicking subcutaneous metastasis at 18F-FDG PET/CT. *Rev Esp Med Nucl Imagen Mol*. 2021;40:255-256. doi:10.1016/j.remn.2020.06.010
48. Martínez Leboráns L, Esteve Martínez A, Victoria Martínez AM, Alegre de Miquel V, Berrocal JA. Cutaneous sarcoidosis in a melanoma patient under Ipilimumab therapy. *Dermatol Ther*. 2016;29:306-308. doi:10.1111/dth.12380
49. McKenna MC, Molloy K, Crowther S, et al. Pembrolizumab-related sarcoid-like reaction presenting as reactivation of

quiescent scars. *J Oncol Pract*. 2018;14:200-201. doi:10.1200/JOP.2017.027383
50. Mitchell MA, Hogan K, Amjadi K. Atezolizumab-induced sarcoid-like granulomatous reaction in a patient with urothelial cell carcinoma. *Immunotherapy*. 2018;10:1189-1192. doi:10.2217/imt-2018-0035
51. Mobini N, Dhillon R, Dickey J, Spoon J, Sadrolashrafi K. Exclusive cutaneous and subcutaneous Sarcoidal granulomatous inflammation due to immune checkpoint inhibitors: report of two cases with unusual manifestations and review of the literature. *Case Rep Dermatol Med*. 2019;2019:1-7. doi:10.1155/2019/6702870
52. Murphy KP, Kennedy MP, Barry JE, O'Regan KN, Power DG. New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. *Oncol Res Treat*. 2014;37:351-353. doi:10.1159/000362614
53. Nishino M, Sholl LM, Awad MM, Hatabu H, Armand P, Hodi FS. Sarcoid-like granulomatosis of the lung related to immune-checkpoint inhibitors: distinct clinical and imaging features of a unique immune-related adverse event. *Cancer Immunol Res*. 2018;6:630-635. doi:10.1158/2326-6066.CIR-17-0715
54. Noguchi S, Kawachi H, Yoshida H, et al. Sarcoid-like granulomatosis induced by Nivolumab treatment in a lung cancer patient. *Case rep Oncol*. 2018;11:562-566. doi:10.1159/000492383
55. Ogawa T, Ishitsuka Y, Iwamoto K, et al. Programmed cell death 1 blockade-induced cutaneous sarcoid-like epithelioid granulomas in advanced melanoma: a case report. *J Eur Acad Dermatology Venereol*. 2018;32:e260-e261. doi:10.1111/jdv.14781
56. Oommen E, Allam J. Ipilimumab Lung Toxicity. *Chest*. 2017;152:A724. doi:10.1016/j.chest.2017.08.753
57. Paolini L, Poli C, Blanchard S, et al. Thoracic and cutaneous sarcoid-like reaction associated with anti-PD-1 therapy: longitudinal monitoring of PD-1 and PD-L1 expression after stopping treatment. *J Immunother Cancer*. 2018;6:52. doi:10.1186/s40425-018-0372-4
58. Person F, Chahoud-Schriefer T, Fehrle W, Janneck M, Huber TB, Wiech T. Severe acute kidney injury due to Nivolumab/Ipilimumab-induced granulomatosis and Fibrinoid vascular necrosis. *J Immunother*. 2020;43:29-31. doi:10.1097/CJI.0000000000000296
59. Reddy SB, Possick JD, Kluger HM, Galan A, Han D. Sarcoidosis following anti-PD-1 and anti-CTLA-4 therapy for metastatic melanoma. *J Immunother*. 2017;40:307-311. doi:10.1097/CJI.0000000000000181
60. Reule RB, North JP. Cutaneous and pulmonary sarcoidosis-like reaction associated with ipilimumab. *J Am Acad Dermatol*. 2013;69:e272-e273. doi:10.1016/j.jaad.2013.07.028
61. Reuss JE, Kunk PR, Stowman AM, Gru AA, Slingluff CL, Gaughan EM. Sarcoidosis in the setting of combination ipilimumab and nivolumab immunotherapy: a case report & review of the literature. *J Immunother Cancer*. 2016;4:94. doi:10.1186/s40425-016-0199-9
62. Rodriguez EF, Lipson E, Suresh K, Cappelli LC, Monaco SE, Maleki Z. Immune checkpoint blocker-related sarcoid-like granulomatous inflammation: a rare adverse event detected in lymph node aspiration cytology of patients treated for advanced malignant melanoma. *Hum Pathol*. 2019;91:69-76. doi:10.1016/j.humpath.2019.07.001
63. Rousseau PM, Raimbourg J, Robert M, Dansette D, Dréno B, Peuvrel L. First case of cutaneous sarcoidosis within tattoos under durvalumab. *Int J Dermatol*. 2019;58:e168-e170. doi:10.1111/ijd.14484
64. Smith RJ, Mitchell TC, Chu EY. Pembrolizumab-induced sarcoidal infusion site reaction. *J Cutan Pathol*. 2018;45:727-729. doi:10.1111/cup.13307
65. Suozzi KC, Stahl M, Ko CJ, et al. Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. *JAAD Case Rep*. 2016;2:264-268. doi:10.1016/j.jdcr.2016.05.002
66. Tan I, Malinzak M, Salama AKS. Delayed onset of neurosarcoidosis after concurrent ipilimumab/nivolumab therapy. *J Immunother Cancer*. 2018;6:77. doi:10.1186/s40425-018-0390-2
67. Tetzlaff MT, Nelson KC, Diab A, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a marker of therapy response in a subset of melanoma patients. *J Immunother Cancer*. 2018;6:14. doi:10.1186/s40425-018-0323-0
68. Tissot C, Carsin A, Freymond N, Pacheco Y, Devouassoux G. Sarcoidosis complicating anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody biotherapy. *Eur Respir J*. 2013;41:246-247. doi:10.1183/09031936.00107912
69. Toumeh A, Sakhi R, Shah S, Arudra SKC, De Las Casas LE, Skeel RT. Ipilimumab-induced granulomatous disease occurring simultaneously with disease progression in a patient with metastatic melanoma. *Am J Ther*. 2016;23:e1068-e1071. doi:10.1097/MJT.0000000000000266
70. Trilleras-Gomez AP, Hull KJ, Drew DZ. Case report and review of 7 similar cases in the literature: cutaneous sarcoidosis as side effect of Pembrolizumab plus chemotherapy in stage IV squamous cell carcinoma of lung. *J Immunother*. 2021;44:90-94. doi:10.1097/CJI.0000000000000351
71. Tulbah RI, Rowe SP, Solnes LB, Javadi MS. Nivolumab-associated pulmonary and bone sarcoidosis in a patient with melanoma of unknown primary. *Clin Nucl Med*. 2019;44:e519-e521. doi:10.1097/RLU.0000000000002724
72. Ung C, Gragoudas E. Checkpoint inhibitor-induced sarcoid choroidal granulomas. *Am J Ophthalmol Case Rep*. 2020;18:100652. doi:10.1016/j.ajoc.2020.100652
73. Van den Eertwegh AJM, Versluis J, Van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol*. 2012;13:509-517. doi:10.1016/S1470-2045(12)70007-4
74. Vogel WV, Guislain A, Kvistborg P, Schumacher TNM, Haanen JBAG, Blank CU. Ipilimumab-induced sarcoidosis in a patient with metastatic melanoma undergoing complete remission. *J Clin Oncol*. 2012;30:e7-e10. doi:10.1200/JCO.2011.37.9693
75. Wang LL, Patel G, Chiesa-Fuxench ZC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. *JAMA Dermatol*. 2018;154:1057-1061. doi:10.1001/jamadermatol.2018.1912
76. Wesselius LJ, DeLeon TT, Gotway MB. A sarcoidlike reaction mimicking metastatic malignancy in a patient with melanoma treated with pembrolizumab. *Am J Roentgenol*. 2018;210:W183-W184. doi:10.2214/AJR.17.19144

77. Wilgenhof S, Morlion V, Seghers AC, et al. Sarcoidosis in a patient with metastatic melanoma sequentially treated with anti-CTLA-4 monoclonal antibody and selective BRAF inhibitor. *Anticancer Res*. 2012;32:1355-1359.
78. Woodbeck R, Metelitsa AI, Naert KA. Granulomatous tumoral melanosis associated with Pembrolizumab therapy: a mimicker of disease progression in metastatic melanoma. *Am J Dermatopathol*. 2018;40:523-526. doi:10.1097/DAD.0000000000001066
79. Yatim N, Mateus C, Charles P. Sarcoidosis post-anti-PD-1 therapy, mimicking relapse of metastatic melanoma in a patient undergoing complete remission. *Rev Med Interne*. 2018;39:130-133. doi:10.1016/j.revmed.2017.11.008
80. Apalla Z, Kemanetzi C, Papageorgiou C, et al. Challenges in sarcoidosis and sarcoid-like reactions associated to immune checkpoint inhibitors: a narrative review apropos of a case. *Dermatol Ther*. 2021;34(1):e14618.
81. Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist*. 2016;21(10):1230-1240. doi:10.1634/theoncologist.2016-0055

How to cite this article: Purcell V, Preti B, Fernandes R. Suspected immune checkpoint inhibitor-induced pulmonary sarcoid reaction in metastatic renal cell carcinoma. *Clin Case Rep*. 2022;10:e05960. doi: 10.1002/ccr3.5960