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

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CASE REPORT

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

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

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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

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A sarcoid reaction is a rare irAE, with only two other cases reported in the treatment of mRCC with immunotherapy. 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 para-tracheal 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...
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 not to 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
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.

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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.

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