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Original Article

Sarcoid-like reactions in patients treated with checkpoint inhibitors for advanced solid tumors

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Abstract

Importance: While new intrathoracic adenopathy in a patient with cancer can represent progression of disease, the differential diagnosis is broad. Sarcoid-like reactions (SLR) remain an underreported source of lymphadenopathy in patients treated with immune checkpoint inhibitors (ICI), with limited reports in patients with cancers other than melanoma.

Objective: To characterize SLRs among patients treated with ICI for advanced solid tumors.

Methods: Data were collected on the clinical, pathologic, and radiographic presentation of patients treated with ICI who developed clinical or imaging findings suggestive of an SLR, including the presence of hilar or mediastinal lymphadenopathy, cutaneous/subcutaneous involvement, and/or worsening of existing sarcoidosis on ICI.

Results: Twelve patients were identified as having experienced an SLR. While 6 patients had melanoma, SLRs were also observed among patients with lung, gynecologic, and genitourinary cancers, including high-grade serous ovarian carcinoma, and an angiomyolipoma. Median time from initiation of ICI to diagnosis of an SLR was 3.4 months (range: 1.8-9.1). All but one patient (92%) were deemed to have had a radiographic response to ICI.

Conclusions and relevance: Clinicians should maintain the awareness of the possibility of SLRs in patients receiving ICI, particularly in patients whose scans show evidence of "mixed" response, with decreases in certain lesions coupled with new/increasing intrathoracic lymphadenopathy and/or other systemic signs of sarcoid.

Key words: sarcoidosis; sarcoid-like reaction; immune checkpoint inhibitors; immunotherapy.

Implications for Practice

This study emphasizes the importance of recognizing sarcoid-like reactions (SLRs) as a potential immune-related adverse event that occurs across a variety of tumor types beyond melanoma, including lung, gynecologic, and genitourinary cancers. Misdiagnosis of SLRs as disease progression risks premature discontinuation of effective immune checkpoint inhibitor (ICI) treatment. Clinicians should be aware of key diagnostic features, including a relatively early onset (between 1.8 and 9.1 months) after treatment initiation, mixed radiographic responses (eg, shrinkage of known tumors alongside new lymphadenopathy), and associated extra-thoracic symptoms such as uveitis or subcutaneous nodules. Although biomarkers such as ACE and eosinophilia may raise suspicion, biopsy remains the gold standard, particularly in cases with intrathoracic manifestations that may mimic disease progression. This is especially relevant in lung cancer patients, where distinguishing SLRs from progression is further complicated by comorbidities such as chronic obstructive pulmonary disease.

Notably, SLRs may correlate with improved response to ICIs, as all but one patient in this series demonstrated radiographic benefit without disease progression at the time of SLR diagnosis. Corticosteroids or immunosuppression were effective in managing SLRs in most cases. However, clinicians should balance the risks of immunosuppression against the benefits of continuing ICIs. This underscores the importance of integrating clinical, radiographic, and pathological data into decision-making processes to optimize patient outcomes. Further research is needed to identify more specific biomarkers for SLRs and to explore the underlying immune mechanisms, ensuring that this phenomenon, now recognized as pan-cancer, is managed effectively without compromising antineoplastic therapy.

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Introduction

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of many advanced solid tumor types.[1,2] Immune checkpoint inhibitors are associated with a diverse set of immune-related adverse effects (irAEs), as well as a unique pattern of disease response known as "pseudo-progression."[2-5] These features of ICI response create diagnostic challenges, as clinicians must distinguish radiographically between inflammatory reactions and true progression of malignancy in order to avoid taking patients off of efficacious therapies prematurely.[6,7] Increased lymphadenopathy can be especially difficult to distinguish due to the wide differential of causative etiologies which include inflammatory reactions and disease progression among many other processes. Sarcoid-like reactions (SLRs), which are defined as the development of lesions that clinically and pathologically mirror those seen in patients with sarcoid following the receipt of immunologically active therapies, can lead to the development of benign mediastinal, hilar, or intrapulmonary inflammation. Sarcoid-like reactions have been described both in patients receiving ICI[8-29] as well as other immunologically active therapies, including highly active antiretroviral therapy, tumor necrosis factor-α antagonists, and interferon therapy.[30-36]

Differentiating SLRs from progressive disease is challenging without biopsies. Drug-induced SLRs may also be localized to various organ systems; SLRs attributed to ICI treatment have most commonly been identified in the lung and skin.[34-36] Whether SLRs in additional locations are truly less common with ICI or whether other areas are simply harder to biopsy and/or more likely to be confused with disease progression remains uncertain.[34-37]

Most cases of SLRs reported following receipt of ICI have been in patients with melanoma.[36] While the preponderance of melanoma cases in the literature may reflect the early adoption of ICI for this disease, it is also notable that there have been several cases of SLRs reported in patients with melanoma who never received ICI, potentially pointing to unique features of the disease's biology.[35,38,39] In recent years, SLRs have been identified following receipt of ICI for additional malignancies,.[8,11,22,27,29,31,40–54] but the number of reported cases remains small and additional investigation is needed to facilitate diagnosis in patients who may have pre-existing malignant hilar and/or mediastinal adenopathy on imaging.

In this paper, we present clinicopathologic data from a series of patients with SLRs following treatment with ICI for a variety of solid tumor types with the aim of investigating distinguishing features of SLRs that can aid clinicians in recognizing the occurrence of these reactions pan-cancer.

Methods

Patients were eligible for inclusion in this case series if they had been seen at Memorial Sloan Kettering Cancer Center between 2015 and 2022 and were identified by their treating physicians as having experienced a possible ICI-associated SLR based on clinical and/or imaging findings. Patients were considered to have an SLR if they had biopsy-proven evidence of sarcoid-like inflammation, including noncaseating granulomas, following receipt of ICI confirmed by a certified pathologist (J.H.). One patient had no tissue available for histopathological assessment; however, this patient had an outside biopsy that was consistent with SLR. Additionally, a patient with a remote diagnosis of sarcoidosis was included in this series given progression of their sarcoidosis in the setting of ICI. This patient had never endorsed any symptoms or required any treatment for their sarcoid prior to receipt of ICI. All scans were reviewed by a certified radiologist (A.W.) specializing in cancer care, including for evidence of hilar and/or mediastinal adenopathy. Clinical and pathologic data were compiled via manual chart review with a data collection cutoff of 7/31/2023. This study was approved by the Institutional Review Board of the Memorial Sloan Kettering Cancer Center.

Results

Patients

We identified 12 patients with SLRs following treatment with ICI, with 11 patients having available tissue for pathologic confirmation (Tables 1-4; Figure 1). Six of these patients were treated for advanced or unresectable melanoma. Additional patients were treated for gynecologic tumors ($n = 2$), including high-grade serous ovarian carcinoma and primary peritoneal carcinosarcoma; nonsmall cell lung carcinoma (NSCLC) ($n = 2$) and genitourinary malignancies ($n = 2$), including clear cell renal carcinoma and epithelioid angiomyolipoma. Treatment regimens included combined PD-1/CTLA4 blockade ($n = 7$), PD-1 blockade monotherapy ($n = 1$), PD-1 blockade with carboplatin and paclitaxel ($n = 3$), or CTLA4 blockade followed by PD-1 blockade ($n = 1$).

One patient had a pre-existing diagnosis of sarcoidosis, identified via lymph node biopsy, in the setting of lymphadenopathy of unknown cause, 15 years prior to receipt of ICI and never previously required treatment. This patient exhibited clinical progression of sarcoid on ICI with the development of pulmonary punctate nodularity and ground glass opacities (GGOs), which had an atypical appearance for metastatic disease. Eleven of the patients who developed an SLR (92%) experienced additional irAEs during treatment, including pneumonitis ($n = 3$), hepatic and/or biliary inflammation ($n = 2$), vitiligo ($n = 2$), arthralgias ($n = 2$), thyroiditis/hypothyroidism ($n = 2$), lichenoid rash ($n = 1$), colitis ($n = 2$), uveitis ($n = 1$), pruritis ($n = 1$), and acute kidney injury (AKI, $n = 1$).

Clinical features of SLRs

Median time from initiation of ICI to SLR diagnosis was 3.4 months (range: 1.8-9.1) (Figure 2). Eleven of the patients (92%) had symptoms attributable to an SLR, including respiratory symptoms (shortness of breath or cough; $n = 8$), cutaneous or subcutaneous lesions ($n = 3$), night sweats ($n = 2$), and uveitis ($n = 2$).

On imaging, mediastinal and/or hilar lesions were seen in 11 of the 12 patients (92%), with the remaining patient exhibiting evidence of pneumonitis (Table 1). Nine patients (75%) had baseline pre-ICI treatment imaging findings suggestive of mediastinal and/or hilar tumor involvement and 3 patients (25%) had biopsy-proven mediastinal and/or hilar tumor involvement. All these patients had evolving intrathoracic changes on imaging at the time of their sarcoid diagnosis, including increased pulmonary nodularity, GGOs, and/or more prominent adenopathy. In 7 of these cases, intrathoracic changes correlating with an SLR were first seen on scans showing a decrease in disease burden in other areas, that is, a mixed pattern. An additional patient with a known diagnosis of sarcoidosis at baseline developed increased GGOs during

Table 1. Characteristics of patients with melanoma.

ID	Age/ Sex	Melanoma subtype / Stage	Tumor involves media-stinum	Immuno-therapy target/clinical response	Time from first IO to sarcoid diagnosis (months)	Sarcoid involvement/ Biopsy indicative of SLR	Symptoms of sarcoid	ACE	AFB	Other irAEs	Disease status at last follow-up	Eosinophilia within 1 month of diagnosis (%)	Received further IO given after sarcoid diagnosis	Received immune suppression for sarcoid involvement?
1	51 F	Unknown primary/ M1b / BRAF V600E	Yes	CTLA4/PD1 × 4/ Yes	1.8	Cutaneous, Hilum/ mediastinum, lung/**Yes**	Cutaneous plaque	N/A	(+)	Pneumo-nitis, hypo-thy-roid, colitis	No evidence of disease. No further treatment received.	Yes (18.8)	Yes	Received steroids for cutaneous sarcoid
2	60 M	Cutaneous/ M1a/ BRAF V600K, TP53	Yes	CTLA4/PD1 × 2/ Yes	5.4	Hilum/mediastinum, lung /**Yes**	Chronic night sweats	168	(–)	Hepatitis, vitiligo	Died; cause unknown. No evidence of disease with no further treatment at last follow-up.	No	No	No; received steroids and mycophenolate mofetil for hepatitis
3	76 M	Cutaneous/ IIIC/ NRAS	No	CTLA4/PD1 × 4/ Yes	3.7	Hilum/mediastinum, lung, spleen/**Yes**	Night sweats, blurred vision/ uveitis	58	(–)	Vitiligo, uveitis, arthral-gias	No evidence of disease. No further treatment received.	No	No	Received steroids for pulmo-nary sarcoid involvement
4	58 M	Cutaneous/ M1b/ Unknown mutations	Yes	CTLA4/PD1 × 1/ Yes	3.4	Hilum/mediasti-num/**Yes**	Dry cough following steroid taper for pneumo-nitis	N/A	(–)	Pneumo-nitis	Surgical manage-ment of disease recurrence 1.6 years after the sarcoid diagnosis. No evidence of disease since.	No	No	Received steroids for granu-lomatous pneumonitis and pulmo-nary sarcoid involvement
5	66 M	Unknown primary/ IIIC/ BRAF D594N	No	PD1 × 4/Adju-vant	3.3	Hilum/mediastinum, enlarged cervical lymph nodes /**Yes**	None	42	(+)	Arthral-gias	Died, cause unknown. POD-spine and brain lesions detected roughly 1.3-year postsarcoid diag-nosis.	Yes (5.2)	No	No; later received steroids for vertebral compression in context of vertebral metastasis
6	54 F	Cutaneous/ IIIC/ NRAS	No	CTLA4 × 4, CTLA4 rein-duction, PD1 thereafter (sar-coid diagnosed after first cycle)/response assessment not available	Unknown	Subcutaneous nod-ules, pulmonary inflammation /N/A—no biopsy specimen available but outside pathol-ogy indicated SLR	Hospital-ized for respiratory symptoms. Had sub-cutaneous nodules.	N/A	N/A	Hepato-biliary toxic-ity, thy-roiditis	Increased thoracic lymphadenopathy that cannot be easily biopsied; unclear whether from sarcoid or melanoma.	No	Yes	Received steroids for pulmonary involvement and later for hepatitis

Abbreviations: AFB= acid fast bacilli testing; IO = immunotherapy; irAE = immune-related adverse events; N/A = not available; POD= progression of disease.

Table 2. Characteristics of patients with gynecological malignancies.

ID	Age/ Sex	Tumor type/ Stage	Tumor involves media-stinum	Immuno-therapy target/clinical response	Time from first IO to sarcoid diagnosis (months)	Sarcoid involvement / Biopsy indicative of SLR	Symptoms of sarcoid	ACE	AFB	Other irAEs	Disease status at last follow-up	Eosinophilia within 1 month of diagnosis (%)	Received further IO given after sarcoid diagnosis	Received immune suppression for sarcoid involvement?
7	59 F	High grade serous ovarian cancer/ IVb	Yes	PD1 × 7 (with chemotherapy), with maintenance PD1 × 3 thereafter/Yes	3.0	Mediastinal nodes /Yes	Cough and dyspnea	N/A	Un-known	Lichenoid rash	Died from disease	No	Yes	Later received steroids for shortness of breath of unclear etiology
8	67 F	History of breast cancer; now with peritoneal high grade carcinosarcoma/IV	Borderline mediastinal nodes present at baseline	PD1 × 4 (with chemotherapy), and maintenance PD1 × 12 thereafter/Yes -> eventual progression on maintenance	Baseline history of asymptomatic sarcoid (previously untreated)	Mediastinal/hilar nodes present from diagnosis, pulmonary ground glass opacities. /Yes	History of shortness of breath; also had large pleural effusions	N/A	(-)	Kidney injury	Died from disease	*Yes (6.1)—measured after imaging of ground glass opacities attributed to sarcoid reactivation vs SLR	Yes	No; received steroid taper for kidney injury

Abbreviations: AFB= acid fast bacilli testing; IO = immunotherapy; irAE = immune-related adverse events.

Table 3. Characteristics of patients with genitourinary malignancies.

ID	Age/ Sex	Tumor type/ Stage	Tumor involves media-stinum	Immuno-therapy target/clinical response	Time from first IO to sarcoid diagnosis (months)	Sarcoid involvement / Biopsy indicative of SLR	Symptoms of sarcoid	ACE	AFB	Other irAEs	Disease status at last follow-up	Eosinophilia within 1 month of diagnosis (%)	Received further IO given after sarcoid diagnosis	Received immune suppression for sarcoid involvement?
9	61 M	Clear cell renal cell carci-noma/ IV	Yes	CTLA4/PD1 × 3/ Yes	2.6	Hilum/media-stinum, lung, pleura /Yes	Baseline pretreat-ment cough, and was on oxygen at night; developed wors-ening SOB	73	(–)	Pneu-moni-tis	Died, cause unknown in setting of COPD and HFpEF exac-erbation. Under-went cytoreductive surgery with no pathologic evidence of disease. No fur-ther treatment with no radiographic evidence of disease.	No	No	Received steroids for pulmo-nary sarcoid involvement and pneumo-nitis
10	71 F	Epithe-lioid Angio-myoli-poma	Yes	CTLA4/PD1 × 4, PD1 × 1/clin-ical improve-ment, with worsening scans	3.3	Mediastinum, skin, kidney. At the time, noted to have pleural nod-ularity and peri-splenic soft tissue /Yes	Worsening SOB, fatigue, skin changes.	72	(–)	None	Believed to have radio-logic progression of disease, but no viable tumor seen on pathology.	Yes (5.5)	No	Received steroids for pulmo-nary sarcoid involvement

Abbreviations: AFB= acid fast bacilli testing; IO = immunotherapy; irAE = immune-related adverse events; N/A = not available.

Table 4. Characteristics of patients with pulmonary malignancies.

ID	Age/ Sex	Tumor type/Stage	Tumor involves media-stinum	Immuno-therapy target/ clinical response	Time from first IO to sarcoid diagnosis (months)	Sarcoid involvement/ Biopsy indicative of SLR	Symptoms of sarcoid	ACE	AFB	Other irAEs	Disease status at last follow-up	Eosinophilia within 1 month of diagnosis (%)	Received further IO given after sarcoid diagnosis	Received immune suppression for sarcoid involvement?
11	61 M	Lung ade-nocar-cinoma/ IV	Yes	PD1 × 2 (alone)/Radio-graphic progression PD1 × 8 (with chemo-therapy), PD1 × 16 (with anti-VEGF), PD1 × 4 (alone)/Yes	9.1	Mediastinal/ hi-lar lymph nodes /Yes	Developed worsening SOB and fatigue over baseline COPD, required hospitalization	N/A	(–)	Pruri-tis	Continues on systemic therapy with stable disease.	No	Yes	Received steroids for COPD exacerbation in setting of pulmo-nary sarcoid
12	57 F	Lung ade-nocar-cinoma/ IV	Yes	CTLA4/PD1 × 2/Yes	4.9	Mediastinal lymph nodes, diffuse sub-cutaneous nodules /Yes	Mild cough, fatigue, skin changes, hospitalized due to hypercalce-mia (16mg/dL) and AKI	132	(IO = immu-nother-apy;)	Coli-tis	No evidence of disease, no further treatment received.	Yes (6.9)	No	Received hydroxy-choloroquine for sarcoid manage-ment

Abbreviations: AFB= acid fast bacilli testing; IO = immunotherapy; irAE = immune-related adverse events; N/A = not available.

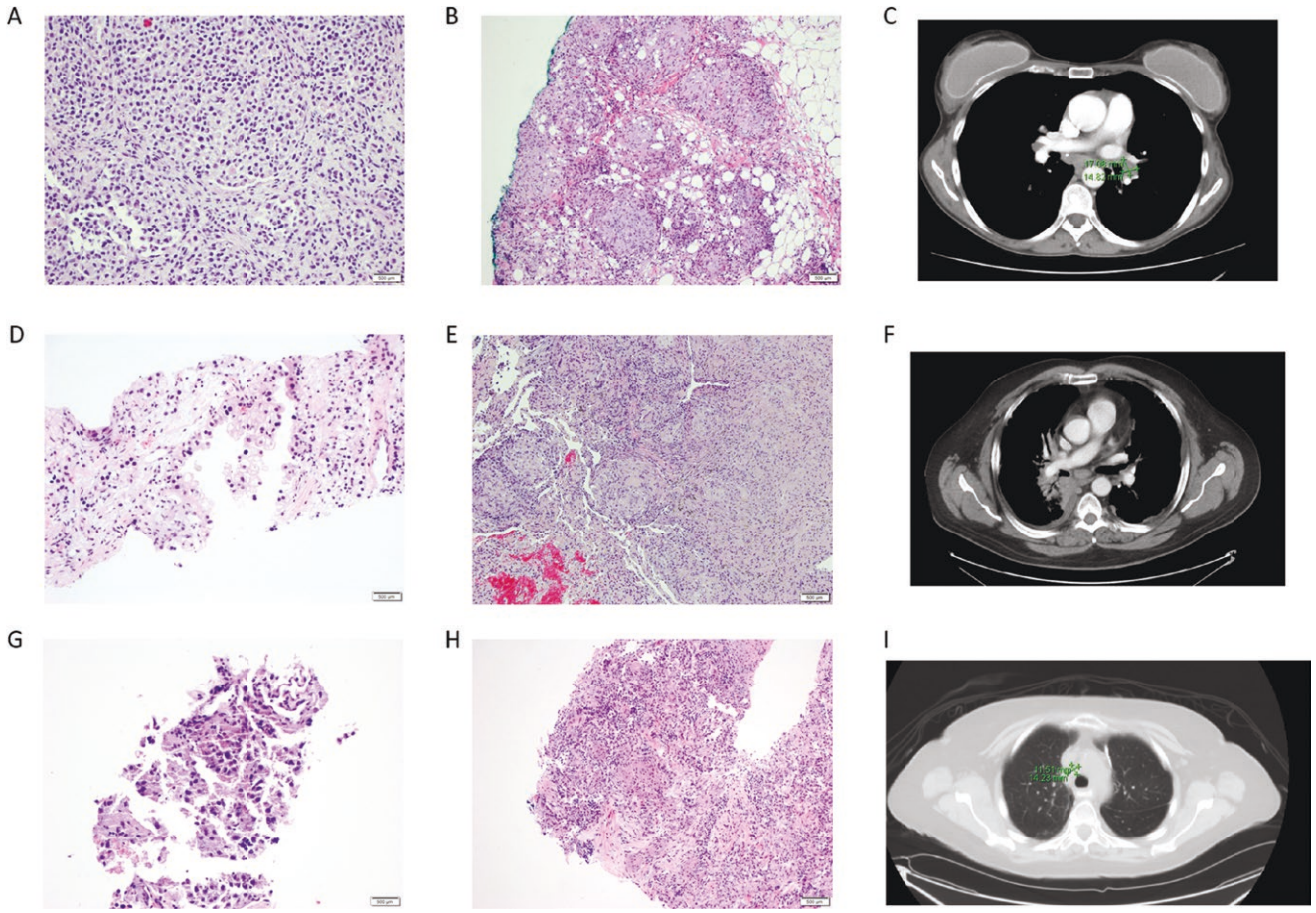

Figure 1. Fifty-one y/o F (subject ID 1) with melanoma, showing representative biopsy specimens from (A) tumor and (B) granuloma, as well as (C) Hilar adenopathy on imaging, and 61 y/o M (subject ID 9) with clear cell renal cell carcinoma, with biopsies showing (D) tumor, (E) noncaseating granulomatous inflammation, and (F) imaging showing hilar adenopathy, and 71 y/o F (subject 10) with epithelioid angiomyolipoma with biopsies showing (G) Tumor, (H) Granuloma, and (I) imaging showing adenopathy.

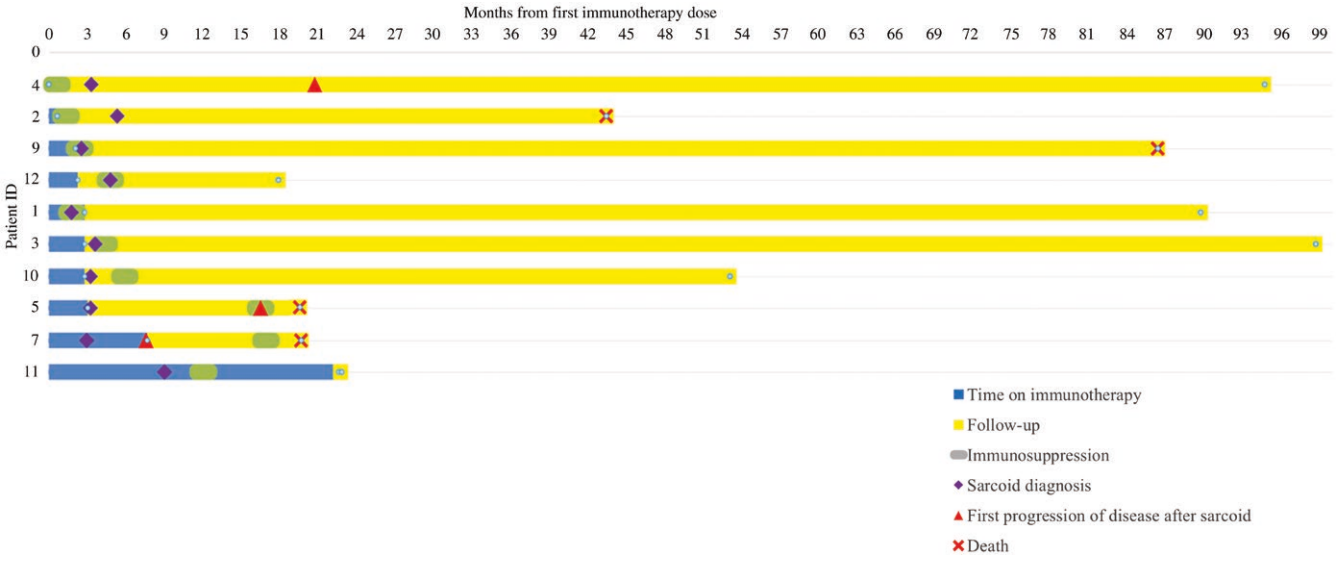

Figure 2. Swimmer's plot showing time from first immunotherapy to sarcoid diagnosis, immune suppressive treatment, and first progression of disease postimmunotherapy. Note that patient ID 4 only received 1 dose of immunotherapy. Subjects who received unpublished experimental therapy, care at an outside facility for which exact dates were unavailable, or who were initially diagnosed with sarcoid prior to commencing immunotherapy are not shown.

treatment that were not biopsied but were suspected to be inflammatory due to the timing of ICI treatment.

Angiotensin converting enzyme (ACE) levels were available for 6 patients; levels ranged from 42 to 168 (median: 72.5; upper limit of normal [ULN] 67 U/L) and were elevated in 4 of the 6 patients. One patient was hospitalized due to hypercalcemia with a serum calcium concentration of 16 mg/dL. This patient also had an AKI at admission, attributed to hypercalcemia and possible SLR involvement. Eosinophilia, defined as a level greater than the ULN (4.9% at our institution), was present within 1 month of diagnosis in 4 of 10 patient (40%) with available data and without prior history of sarcoidosis. Additionally, the patient with a prior diagnosis of asymptomatic sarcoidosis exhibited eosinophilia after development of GGOs. Four patients had a positive acid-fast bacillus (AFB) stain on bronchoscopy, while 6 had a negative AFB stain and 2 patients had no AFB stain results available.

Management of SLRs

In most cases (58%; $n = 7$), immunotherapy was permanently discontinued after diagnosis of an SLR. Six patients (50%) had ICI discontinued due to pulmonary SLRs and associated symptoms. One patient (8%) had therapy withheld due to hepatotoxicity at the time of SLR diagnosis and believed to be a separate irAE. All patients who discontinued ICI treatment exhibited radiographic responses to ICI treatment and were placed on active observation after treatment discontinuation. Five patients (42%) continued ICI treatment following the SLR diagnosis.

The median follow-up from SLR diagnosis to the end of study was 43.6 months (range 13.0-94.3 months). Four patients (33%), 3 with melanoma and 1 with NSCLC, exhibited no signs of progression at last follow-up and required no further cancer-directed therapy. One patient with melanoma received surgical management for recurrence 1.6 years after SLR diagnosis and subsequently exhibited no evidence of disease. The 2 patients with genitourinary malignancy also underwent surgical management for possible disease recurrence; however, no pathologic evidence of disease was found in both these cases.

Five patients (42%) eventually developed radiographic progression of disease following ICI. However, one of the patients with suspected radiographic progression was later found to have no evidence of disease on biopsy, with no viable tumor seen on pathology. Four patients (33%) were ultimately determined to have definitive progression of their cancer and 2 patients (17%) remained on systemic chemotherapy as of last follow-up. Two patients died from their disease, while 3 additional patients passed away from unknown causes with limited available records. Two of these patients had no known evidence of disease at the time of death and 1 had known brain and spine metastases.

Overall, 7 patients (67%) received steroids for known, tissue proven SLRs or for pulmonary symptoms and inflammation attributed to an SLR. This included 3 of the 5 patients who continued ICI after the SLR diagnosis. One of the patients who received steroids for shortness of breath had received both ICI and gemcitabine, the latter of which can be associated with pneumonitis as well.[55] Additional indications for immunosuppressive treatment included hepatitis ($n = 1$), immune-mediated AKI ($n = 1$), vertebral compression fracture ($n = 1$), and an exacerbation of existing chronic obstructive pulmonary disease (COPD), believed to be triggered by an SLR ($n = 1$). One patient who continued ICI treatment after SLR diagnosis also received hydroxychloroquine for SLR management after eventual discontinuation of ICI.

Discussion

We present clinicopathologic data from patients with a variety of different tumor types who experienced SLRs following receipt of ICI. Given that SLRs can be radiographically mistaken for progression of disease, this case series affirms the importance of maintaining a high index of suspicion for SLRs. Because the preponderance of the literature on SLRs has focused on patients with melanoma,[8-21,23-26,28,29] there has been a suggestion that patients with melanoma may be especially prone to SLRs.[35,38,56] The present series highlights that SLRs can occur across a variety of tumor types following ICI and offers additional information on the disease course of patients who develop this treatment-related complication.

Sarcoid-like reactions following ICI are likely underreported. In a single center series of 908 patients who received anti-PD-1 or PD-L1 therapy, with or without CTLA-4 blockade, SLR incidence was estimated to be as low as 0.2% ($n = 2$).[57] However, in a separate single center study analyzing radiographic irAEs in 147 patients with advanced melanoma, up to 5% patients treated with the CTLA-4 blocking agent ipilimumab demonstrated sarcoid-like adenopathy, suggesting a higher incidence of SLRs than previously recognized.[12]

The present series highlights that SLRs can occur following ICI in gynecologic and genitourinary tumors as well as in primary lung tumors. Sarcoid-like reactions due to ICI treatment have previously been reported in renal cell carcinoma, urothelial, uterine, ovarian, and prostate cancers.[22,40–46] This series expands upon this existing landscape by providing descriptions of ICI-associated SLRs in 2 histologies that, to our knowledge, have not previously been reported, namely: epithelioid angiomyolipoma and high-grade serous ovarian carcinoma. We also describe the first case of ICI-associated sarcoid flare in a patient with primary peritoneal carcinosarcoma who had a baseline of asymptomatic sarcoidosis.

In this series, we reported 2 SLRs in patients with lung cancer. It is notable that few lung cases have been previously reported,[8,11,58,59] despite the frequent use of ICI for the disease. Moreover, those previously reported have tended to exhibit extrathoracic manifestations of SLR.[8,60] Given that both patients with lung cancer in this cohort exhibited intrathoracic manifestations, confirmed by biopsy, it is possible that the dearth of reported SLRs in lung cancers may partly be due to the challenges of differentiating between an SLR and malignant progression in these patients, including due to comorbidities such as COPD in this population.[8-11]

For clinicians, differentiating between an SLR and progression of disease is critical. Our series highlights several key clinical features that can help make this distinction. First, in our series, cases of an SLR were diagnosed between 1.8 and 9.1 months after starting treatment. Several patients had simultaneous development of extrathoracic symptoms such as uveitis and/or subcutaneous nodules that increased suspicion for an SLR. Patients that solely exhibit intrathoracic manifestations of an SLR are at risk for being missed and/or labeled as having progressive disease. For these patients, mixed radiographic response, such as shrinking of known tumors in the context of new lymphadenopathy, may help raise suspicion.[58]

Blood-based biomarkers were imperfect for diagnosis in our cohort. For classic sarcoidosis, the most widely used biomarker is serum ACE, which is elevated in 30%-80% of patients.[61] A number of other biomarkers, including levels of lysozyme, neopterin, and soluble Interleukin-2 receptor, have been explored but have limited sensitivity and specificity.[61] In our series, 4 of 6 patients with available testing had elevated ACE levels. Although elevated ACE levels may raise suspicion for an SLR, biopsy remains the gold standard for SLR diagnosis, as ACE can be elevated in other inflammatory conditions leading to intrathoracic adenopathy such as tuberculosis.[61,62] We also looked at eosinophilia as a potential biomarker, as this has been reported in association with sarcoidosis.[63] However, excluding the patient with a previous sarcoid diagnosis, eosinophilia was only present in 4 patients. Furthermore, eosinophilia secondary to ICI treatment is well documented, limiting the utility of this measure in identifying SLRs.[64] Additional studies are needed to refine biomarkers of SLRs.

In addition to examining diagnostic clues, we also analyzed the disease course of patients with SLRs following ICI. Prior research has established that patients who develop certain irAEs, such as vitiligo, are more likely to benefit from ICI.[65] In keeping with a recently published series in which sarcoid-like granulomatosis was associated with improved overall survival, all but one patient in our series was deemed to have radiographic benefit from ICI.[26] None of the patients in our series had progression of disease at the time of their SLR. In terms of management, most patients in our cohort received treatment with corticosteroids for SLRs or symptoms thought to be related to the SLR. Many patients also received immunosuppression for additional irAEs at some point following ICI. Such treatments for other irAEs may have also damped down further sarcoid-like inflammation.

This study has several limitations. First, it represents a retrospective, single-center case series. While the number of patients reported is modest, our cohort constitutes one of the largest series of patients with SLRs after immunotherapy reported to date and includes the first reports of SLRs in epithelioid angiomyolipoma and high-grade serous ovarian carcinoma. Second, several patients had pretreatment staging scans with mediastinal and/or hilar adenopathy. While we cannot exclude the possibility that some of these patients had undiagnosed sarcoid prior to receiving immunotherapy, it is also possible that SLRs occurred in areas with contemporaneous tumor involvement. Indeed, in one case, a mediastinal node was excised post-ICI treatment and demonstrated sarcoid-like noncaseating granulomatous inflammation co-existent with malignant cells. Lastly, we cannot rule out the possibility that these patients had other predisposing factors, since even certain chemotherapies have been associated with SLRs and since at least one patient in our series had a prior negative work-up for sarcoid before starting treatment.[36]

Overall, our pan-cancer series underscores that SLRs can occur in a variety of tumor types beyond melanoma. It also highlights the fact that maintaining an awareness of the possible involvement of SLRs in patients with new or progressive intrathoracic lesions on imaging who otherwise respond to ICI is critical to in order to avoid unnecessary discontinuation of potentially effective antineoplastic therapy. By identifying patients who developed SLRs during treatment for a variety of advanced solid tumors, this report emphasizes that sarcoidosis associated with immunotherapy is a more widespread phenomenon pan-cancer than previously recognized. Further work is necessary to identify potential biomarkers for the development of SLRs and to elucidate underlying immune-mediated mechanisms.

Author contributions

Ian Nykaza (Data curation, Formal Analysis, Investigation, Writing—review & editing), Yonina R. Murciano-Goroff (Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing—original draft, Writing—review & editing), Antoine Desilets (Data curation, Formal analysis, Writing—review & editing), Guilherme Harada (Data curation, Investigation, Writing—review & editing), Michael A. Postow (Data curation, Investigation, Writing—review & editing), Margaret K. Callahan (Data curation, Formal analysis, Investigation, Writing—review & editing), Chung-Han Lee (Investigation, Writing—review & editing), Charles M Rudin (Investigation, Methodology, Resources, Writing—review & editing), David Paul Kelsen (Conceptualization, Investigation, Resources, Validation, Writing—review & editing), Zsofia K Stadler (Investigation, Writing—review & editing), Andreas G Wibmer (Investigation, Validation, Writing—review & editing), Jacyln F Hechtman (Investigation, Writing—review & editing), Alexander Drilon (Data curation, Investigation, Resources, Supervision, Writing—review & editing), and Claire F. Friedman (Conceptualization, Data curation, Investigation, Resources, Supervision, Writing—review & editing)

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Study conduct was approved by the Institutional review committee.

Consent for publication

Not required.

Conflicts of interest

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C.M.R. has consulted regarding oncology drug development with AbbVie, Amgen, Astra Zeneca, D2G, Daiichi Sankyo, Epizyme, Genentech/Roche, Ipsen, Jazz, Kowa, Merck, and Syros. He serves on the scientific advisory boards of Auron, Bridge Medicines, DISCO, Earli, and Harpoon Therapeutics.

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Data Availability

Data are available on reasonable request. All data relevant to the study are included in the article. The corresponding author may be contacted with any requests.

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