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REVIEW ARTICLE

Immune checkpoint inhibitor-induced sarcoidosis-like granulomas

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Abstract

Immune checkpoint inhibitors targeting the cytotoxic T lymphocyte-associated antigen-4 and programmed cell death-1 receptors have transformed the treatment of melanoma and other cancers. These therapies are associated with a number of side effects, including immune-related adverse events. Sarcoidosis-like granulomas (SLGs) are important immune checkpoint inhibitor-related reactions to recognize as SLGs can mimic disease progression and accordingly impact treatment decisions. We systematically review reports of immune checkpoint inhibitor-induced SLGs in cancer patients and discuss potential underlying pathophysiological mechanisms.

Keywords Drug reactions · Melanoma · Immune checkpoint inhibitor · PD-1 · CTLA-4 · Sarcoidosis-like granuloma

Abbreviations

BAL	Bronchoalveolar lavage
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
IFN-γ	Interferon gamma
IL	Interleukin
iRAEs	Immune-related adverse events
NR	Not reported
PD-1	Programmed death-1
SLG	Sarcoidosis-like granuloma
TCR	T-cell receptor
Th-1	T helper-1
Th-17	T helper-17
TNF-α	Tumor necrosis factor alpha

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Introduction

Immune checkpoint inhibitors, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) inhibitors, are now considered first-line treatment for advanced melanoma patients. PD-1 inhibitors, in particular, are also successful in treating a myriad of other tumor types, including non-small cell lung cancer, head and neck squamous cell carcinoma, renal cell carcinoma, and Hodgkin lymphoma [1–4].

CTLA-4 acts by blocking co-stimulatory signals required for T-cell activation, thereby preventing self-reactive T-cell responses and ultimately promoting peripheral tolerance of tumor antigens. CTLA-4 inhibitors, like ipilimumab, result in non-specific T-cell activation and anti-tumor immune responses [5]. PD-1 is a major regulator of chronically activated T-cells, as it is induced on both $CD4^+$ and $CD8^+$ T-cells. PD-L1 and PD-L2, the ligands of the PD-1 receptor, are expressed on many types of cancers, including 31–44% of melanomas [6, 7]. Binding of PD-1 to its physiologic ligands, PD-L1 or PD-L2, suppresses the activation and function of T-cells through recruitment of downstream signaling molecules that ultimately facilitate immune evasion of tumor cells [8]. The PD-1 inhibitors nivolumab and pembrolizumab predominantly act to reverse the suppression of anti-tumor T-cells, thus potentiating anti-tumor immune responses [8].

Thorough descriptions of the adverse effects of immune checkpoint inhibitors are of paramount importance given their widespread utility in cancer therapy. Immune-related adverse events (iRAEs) are common and reported to affect nearly every organ in the body, ranging from non-specific thyroiditis, pneumonitis, and dermatitis, to other autoimmune conditions [9, 10]. Sarcoidosis-like granulomas (SLGs) are non-caseating epithelioid granulomas found in the absence of systemic sarcoidosis, and are one type of iRAE reported in patients receiving immune checkpoint inhibitor therapy. Formation of SLGs is clinically significant as they can simulate disease recurrence, leading to cessation of potentially life-saving immunotherapy. To highlight this important iRAE and to explore its potential etiology, we report results from a Prisma-guided systematic review of cases of SLGs induced by CTLA-4 and PD-1 inhibitors including a case from our institution.

Methods

In accordance with PRISMA guidelines, PubMed was searched through February 4, 2019 without time and language restrictions. Keyword search terms are presented in Tables 1, 2, and 3. All study types were included in the data search. Additional studies were obtained from reviewing the references of relevant studies. From the search, 88 records were identified and 54 original studies were reviewed for study eligibility after duplicate records were removed (Fig. 1). Only sarcoidosis-like adverse effects occurring in cancer patients treated with a CTLA-4 inhibitor, a PD-1 inhibitor, or a combination of both were included. Data extracted from eligible studies included patient demographics, including age and sex, type of cancer, type of checkpoint inhibitor used and dosage, time to SLG onset, affected organs, management, clinical outcomes, and time to resolution, if applicable.

Results

We identified a total of 55 SLG cases, including one case from our institution. Tables 1, 2, and 3 summarize the demographics and clinical characteristics of patients with SLGs [10–50]. The mean age of patients was 58 years (range 26–81 years). Of the cases reporting sex, 53% occurred in men. Of the 55 cases, only one patient was reported to have a known history of sarcoidosis prior to treatment and development of SLGs. The underlying cancers included: melanoma (78%), lung cancer (11%), Hodgkin lymphoma (4%), uterine leiomyosarcoma (2%), gallbladder cancer (2%), renal cell carcinoma (2%), and prostate cancer (2%). Of the SLG cases, 45% occurred in patients receiving PD-1 inhibitors, 27% occurred in patients receiving sequential or combination PD-1/CTLA-4 inhibitors, and 27% occurred in patients receiving CTLA-4 inhibitors. In the 29 cases reporting time from initiating immune checkpoint inhibitor treatment to SLG development, the mean was 8.7 months (range 0.75–22.5 months).

SLGs most commonly involved the lymph nodes, lungs, and skin; less commonly, the central nervous system, pituitary gland, spleen, and bone were affected. Lymph node SLGs were observed in 71% of cases. Lung involvement was observed in 60% of cases and included bilateral parenchymal patchy ground glass opacities with septal thickening, as exemplified in our patient (Fig. 2a–c). Cutaneous findings were noted in 54.5% of cases and included subcutaneous nodules, most commonly, as well as skin-colored papules and plaques on the face, neck, and arms [39, 45]. Ocular findings occurred in four patients and included dry-eye syndrome, acute iritis, retinochoroiditis, and panuveitis with multifocal choroiditis [22, 24, 27, 32]. Brain involvement included neurologic symptoms that prompted MRI imaging revealing leptomeningeal enhancement with adjacent areas of parenchymal enhancement in three patients [19, 47, 48]. Spleen and bone SLG involvement were rare, noted in one patient each.

In 22% of SLG cases, there was initial concern for tumor progression upon patient presentation; the SLGs were ultimately confirmed by biopsies. To treat the SLGs, most patients required discontinuation of therapy completely or for a short period of time as well as immunosuppressant treatment. In cases where outcomes were reported (89%), resolution occurred within a mean of 4 months (range 0.5–24 months), and the SLGs resolved in all but nine patients. Of the patients with SLGs that resolved, 41% resolved with a brief holiday or full discontinuation of immune checkpoint inhibitor therapy alone; 41% resolved with a brief holiday or full discontinuation of immune checkpoint inhibitor therapy and steroids (or additional immunosuppressant therapy); 5% resolved with steroids alone; and 13% resolved with no treatment. Topical and intralesional steroids were required for resolution of cutaneous SLGs in four cases. Ocular findings in two patients required treatment with oral corticosteroids and topical corticosteroid eye drops. In two cases of CNS SLGs, increased steroid dosage and duration as well as additional immunosuppressants including infliximab and methotrexate were required to achieve resolution of neurological symptoms and MRI changes.

Discussion

Sarcoidosis is a systemic granulomatous disease characterized by a hyperactive T helper-1 (Th-1) immune response that results in the formation of non-caseating granulomas in addition to bilateral hilar lymphadenopathy. The

Table 1 Sarcoidosis-like granulomas induced by CTLA-4 inhibitor, ipilimumab

References	Age, sex (M/F)	Cancer	Immune checkpoint inhibitor used[a]	Time to onset[b]	Affected organs	ICI stopped	Immunosuppression used[a]	SLG resolved?	Time to resolution (mos)
Eckert et al. [11]	67, F	Melanoma	Anti-CTLA-4 antibody q3 wks for 3 mos, followed by ipilimumab 3 mg/kg q3 wks	7 mos	LN, lung, skin	Y	None	Y	3
Berthod, et. al [12]	63, M	Melanoma	Ipilimumab 3 mg/kg q3 wks	3.3 mos	Lung	N	Prednisone 1.5 mg/kg/d for 4 wks	Y	3
Van den Eertwegh, et. al [13]	NR	Prostate	Ipilimumab 3 mg/kg q3 wks + GVAX	3 cycles	Lung	Y	High dose prednisone taper for 3 mos + GVAX	Y	3
Vogel et al. [14]	49, M	Melanoma	Ipilimumab 3 mg/kg q3 wks	4 cycles	LN	N	None	Y	4
Wilgenhof et al. [15]	48, F	Melanoma	Ipilimumab 3 mg/kg q3 wks	1 month	LN, lung	Y	Methylprednisolone 48 mg/d for 6 wks	Y	4
Reule and North [16]	55, M	Melanoma	Ipilimumab 10 mg/kg	2 cycles	LN, lung, skin	Y	Prednisone	Y	NR
Tissot et al. [17]	57, M	Melanoma	Ipilimumab 10 mg/kg q3 wks, then q12 wks thereafter	6 cycles	LN, lung, skin	Y	None	Y	5
Andersen et al. [18]	44, M	Melanoma	Ipilimumab 3 mg/kg q3 wks	22.5 mos	Spleen	N	None	Y	6
Murphy et al. [19]	37, M	Melanoma	Ipilimumab 3 mg/kg q3 wks	4 mos	LN, brain, lung	Y	Prednisone 40 mg/d for 4 wks	Y	3
Firwana et al. [20]	57, F	Melanoma	Ipilimumab	2 cycles	LN, skin	NR	NR	NR	NR
Martinez et al. [21]	46, F	Melanoma	Ipilimumab 3 mg/kg	4 cycles	Lung, skin	Y	Topical: clobetasol Oral: prednisone	Y: skin N: pulmonary	NR
Toumeh et al. [22]	26, M	Melanoma	Ipilimumab 3 mg/kg q3 wks	1 month	LN, skin, lung	Y	Prednisone 60 mg/d for 7 wks[c]	Y	2
Nandavaram et al. [23]	54, F	Melanoma	Ipilimumab	3 cycles	LN	Y	None[d]	Y	6
Tetzlaff et al. [40]	44, F	Melanoma	Ipilimumab 3 mg/kg	NR	LN, skin	N	None	Y	8
	79, M	Melanoma	Ipilimumab, then pembrolizumab 2 mg/kg q3 wks[e]	20 mos	LN, skin	Y	Intralesional triamcinolone	Y	3

M male, *F* female, *ICI* immune checkpoint inhibitor, *SLGs* sarcoidosis-like granulomas, *mos* months, *q* every, *wks* weeks, *mg* milligrams, *kg* kilograms, *LN* lymph nodes, *Y* yes, *N* no, *d* day, *NR* not reported, *GVAX* granulocyte–macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine

[a]Dose indicated if reported

[b]Some studies reported time to onset of SLGs in months; others reported number of treatment cycles rather than time

[c]Patient required ophthalmic 1% prednisolone drops for a non-SLG side effect of paramacular immune-mediated retinochoroiditis that occurred 1 week after the second dose of ipilimumab

[d]Patient required ophthalmic and oral steroids for a non-SLG side effect of blepharitis that occurred after the second cycle of ipilimumab

[e]Patient developed LN and skin SLGs after single-agent ipilimumab therapy. Pembrolizumab was later introduced due to disease progression on ipilimumab

Table 2 Sarcoidosis-like granulomas induced by PD-1 inhibitors, pembrolizumab and nivolumab

References	Age, sex (M/F)	Cancer	Immune checkpoint inhibitor used[a]	Time to onset[b]	Affected organs	ICI stopped	Immunosuppression used[a]	SLGs resolved?	Time to resolution
Cotliar et al. [24]	72, F[c]	Hodgkin lymphoma	Pembrolizumab 200 mg q3 wks	6 mos	LN, bone, lung, skin, eye	Y	Prednisone 60 mg/d	Y	1 month
Cousin et al. [25]	55, F	Uterine leiomyosarcoma	Pembrolizumab + cyclophosphamide	1.5 mos	LN, lung	Y	None	Y	NR
Danlos et al. [26]	57, M	Melanoma	Nivolumab 3 mg/kg q2 wks	10 mos	LN, lung, skin	Y	None	Y	12 mos
Montaudie et al. [27]	56, M	Melanoma	Nivolumab 3 mg/kg q2 wks	0.75 month	Lung, bronchus, parotid gland	Y	Prednisone 0.75 mg/kg/d	Y	1 month
Birnbaum et al. [28]	63, F	Lung adenocarcinoma	Nivolumab 3 mg/kg q2 wks	7 cycles	Skin	Y, B	Topical: fluocinonide 0.05% and hydrocortisone 2.5% Oral: prednisone 10 mg/d and hydroxychloroquine 200 mg BID	SD	1 month
Burillo-Martinez et al. [29]	60, F	Melanoma	Pembrolizumab 2 mg/kg q2 wks	3 cycles	LN, skin	Y, B	Prednisone 0.75 mg/kg/d	Y	2 mos
Fakhri et al. [30]	74, M	Small cell lung adenocarcinoma	Pembrolizumab + carboplatin/pemetrexed	6 cycles	LN	NR	NR	NR	NR
Lainez et al. [31]	69, M	Non-small cell lung adenocarcinoma	Nivolumab 3 mg/kg q2 wks	8 cycles	LN	N	None	SD	NA
Le Burel et al. [10]	61, M	Gallbladder adenocarcinoma	PD-1 inhibitor[d]	1 cycle	LN, lung	N	Cyclosporine 0.5 mg/kg/d	Y	NR
	71, F	Melanoma	PD-1 inhibitor[d]	10.5 mos	LN, skin	N	None	Y	NR
Lise et al. [32]	68, F	Melanoma	Pembrolizumab	6 mos	LN, lung, eye	NR	NR	NR	NR
Lomax et al. [33]	57, F	Melanoma	Pembrolizumab	4 cycles	LN, skin lung	Y, B	None	Y	2 mos
	65, F	Melanoma	Pembrolizumab	9 cycles	LN, skin, lung	Y	Prednisone 30 mg/d	Y	NR
Zhang et. al [34]	64, F	Renal cell carcinoma	Nivolumab	10 mos	LN	NR	NR	NR	NR
Dimitriou et al. [35]	57, M	Melanoma	Nivolumab or ipilimumab[e]	3 mos	LN, skin	N	Topical mometasone furate	Y	6 mos

Table 2 (continued)

References	Age, sex (M/F)	Cancer	Immune checkpoint inhibitor used[a]	Time to onset[b]	Affected organs	ICI stopped	Immunosuppression used[a]	SLGs resolved?	Time to resolution
	65, M	Melanoma	Pembrolizumab[f]	1 month	LN, skin	N	Topical: steroids Oral: prednisolone 20 mg/d	Y	2 wks
Laroche et al. [36]	68, F	Melanoma	Nivolumab 3 mg/kg q2 wks[g]	4 cycles	LN, lung, skin	N	None	SD	NA
Nishino et al. [37]	29, M	Hodgkin lymphoma	Nivolumab 3 mg/kg q2 wks and lirilumab 3 mg/kg q4 wks	20.7 mos	Lung	Y, B	None	Y	2 mos
	61, F	Lung adenocarcinoma	Pembrolizumab 200 mg q3 wks	8 mos	Lung	Y, B	None	Y	2 mos
Noguchi et al. [38]	81, M	Pleomorphic carcinoma of lung	Nivolumab	4 cycles	Lung	Y	None	Y	6 mos
Smith et al. [39]	61, M	Melanoma	Pembrolizumab	3 mos	LN, skin	Y	None	Y: LN N: skin[h]	NR
Tetzlaff et al. [40]	68, M	Melanoma	Pembrolizumab 2 mg/kg	6 mos	LN	N	None	Y	2 mos
Wang et al. [41]	60, M	Melanoma	Pembrolizumab	12 mos	Skin, lung	NR	NR	NR	NR
Woodbeck et al. [42]	64, M	Melanoma	Pembrolizumab	2 mos	Skin	NR	NR	NR	NR
Lu [50]	80, M	Melanoma	Pembrolizumab	18 mos	LN, skin	Y	None	Y	12 mos

M male, *F* female, *ICI* immune checkpoint inhibitor, *SLGs* sarcoidosis-like granulomas, *mos* months, *mg* milligrams, *q* every, *wks* weeks, *LN* lymph node, *d* day, *Y* yes, *NR* not reported, *kg* kilogram, *B* brief ICI holiday, *BID* twice a day, *SD* stable disease, *N* no, *NA* not applicable

[a]Dose indicated if reported

[b]Some studies reported time to onset in months, while others did not specify time in months and instead reported number of immune checkpoint inhibitor cycles

[c]Patient had a prior history of sarcoidosis

[d]This study did not distinguish which PD-1 inhibitor was administered

[e]Patient was enrolled in ipilimumab vs. nivolumab clinical trial (BMS 238 study, NCT02060188). It is not known which drug the patient received

[f]Patient was enrolled in pembrolizumab and epacadostat/placebo keynote- 252 study, NCT02752074

[g]Patient developed pulmonary sarcoidosis after single-agent nivolumab therapy. Ipilimumab was later introduced due to disease progression on nivolumab

[h]Skin SLGs initially resolved upon discontinuation of pembrolizumab but recurred 5 months later. LN SLGs completely resolved

etiology of sarcoidosis remains unclear, though the Th-1 predominant immune response is thought to be initiated by the phagocytic response of CD4$^+$ Th-1 cells encountering foreign antigens [51]. The subsequent adaptive immune response that ensues prompts the release of Th-1-specific pro-inflammatory cytokines, including interferon-γ (IFN-γ), interleukin (IL)-2, IL-12, IL-18, and tumor necrosis factor alpha (TNF- α) [51]. Ultimately, the Th-1-predominant cytokine profile is the stimulus for subsequent macrophage aggregation and activation, the hallmarks of granulomatous inflammation. The activated macrophages within the pro-inflammatory cytokine milieu additionally serve to recruit IL-17-producing T helper-17 (Th-17) cells. Increased IL-17 is reported in sarcoidal granulomas, where it is thought to play a role in the formation and maturation of granulomas [52].

Increased Th-17 cells may also be associated with the SLGs induced by immune checkpoint inhibitors. Studies have demonstrated that CTLA-4 blockade results in increased Th-17 CD4$^+$ cells in peripheral blood in melanoma patients, thus leading to an extended production of pro-inflammatory molecules, including IL-6 and TNF-α, believed to lead to SLG development [53]. PD-1 inhibition, via checkpoint inhibitors nivolumab or pembrolizumab,

Table 3 Sarcoidosis-like granulomas induced by combination or sequential CTLA-4/PD-1 inhibitor therapy

References	Age, sex (M/F)	Cancer	Immune checkpoint inhibitor used[a]	Time to onset[b]	Affected organs	ICI stopped	Immunosuppression used[a]	SLGs resolved?	Time to resolution
Firwana et al. [20]	37, F	Melanoma	Ipilimumab 4 cycles, then pembrolizumab	6 cycles	LN, lung, skin	Y	None	Y: lung, skin SD: LN	2 mos
Koelzer et al. [43]	35, F	Melanoma	Ipilimumab 3 mg/kg q3 wks, then nivolumab 3 mg/kg q2 wks	Ipilimumab: 4 cycles Nivolumab: 4 cycles	Lung	N	None	Melanoma related death	NA
Reuss et al. [44]	32, F	Melanoma	Ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3 wks	4 cycles	LN, skin	Y, B	None	SD	NR
Suozzi et. al [45]	60, F	Lung adenocarcinoma	Ipilimumab 1 mg/kg q6 wks + nivolumab 1 mg/kg q2 wks	7 mos	Skin	N	Topical clobetasol 0.05% ointment	Y	2 wks
Lomax et al. [33]	44, M	Melanoma	Nivolumab, then ipilimumab	NR	LN, skin, lung	N	Infliximab Prednisolone 30 mg/d	SD	NR
Reddy et al. [46]	55, F	Melanoma	Ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3 wks	4 cycles	LN, lung, skin	Y, B	Prednisone 60 mg/d for 1 month	Y	2 wks
	57, F	Melanoma	Ipilimumab 3 mg/kg q3 wks, then pembrolizumab[c]	8 cycles[d]	LN, lung, skin	Y, B	Dexamethasone 18 mg TID tapered over 3 wks	Y	1 month
Dimitriou et al. [35]	72, M	Melanoma	Ipilimumab, then pembrolizumab	22 mos	Skin	N	None	N	NA
	73, M	Melanoma	Ipilimumab, then pembrolizumab	15 mos	LN, lung	N	None	N	NA
Dunn-Pirio et al. [47]	68, M	Melanoma	Ipilimumab + nivolumab	2 cycles[e]	LN, lung, brain	Y	Dexamethasone Infliximab 5 mg/kg for 3 doses MTX 12.5 mg/wk	Y	24 mos
Nishino et al. [37]	65, F	Melanoma	Nivolumab + ipilimumab, then pembrolizumab 2 mg/kg q3 wks	11.3 mos	Lung	B	None	Y	1 month
	74, M	Melanoma	Ipilimumab, then pembrolizumab 2 mg/kg q3 wks	14.3 mos	Lung	B	None	Y	4 mos

Table 3 (continued)

References	Age, sex (M/F)	Cancer	Immune checkpoint inhibitor used[a]	Time to onset[b]	Affected organs	ICI stopped	Immunosuppression used[a]	SLGs resolved?	Time to resolution
Tan et al. [48]	65, M	Melanoma	Ipilimumab 3 mg/kg + nivolumab 1 mg/kg	2 cycles	LN, brain	Y	Dexamethasone 16 mg for 4 mos Infliximab 5 mg/kg Methylprednisolone 125 mg for 3 wks MTX 12.5 mg/wk[f]	Y	4 mos
Yatim et. al [49]	72, NR	Melanoma	Ipilimumab 3 mg/kg, then pembrolizumab 2 mg/kg q3 wks	Ipilimumab: 2 cycles Pembrolizumab: 8 cycles	LN, skin, lung	B	None	Y	3 mos
Our case	36, F	Melanoma	Ipilimumab 3 mg/kg q3 wks, 7 cycles, then pembrolizumab 2 mg/kg q3 wks	5 mos	LN, lung	Y	None	Y	5 mos

M male, *F* female, *ICI* immune checkpoint inhibitor, *SLGs* sarcoidosis-like granulomas, *LN* lymph nodes, *Y* yes, *SD* stable disease, *mos* months, *mg* milligram, *kg* kilogram, *q* every, *wks* weeks, *N* no, *NA* not applicable, *B* brief ICI holiday, *NR* not reported, *d* day, *TID* three times a day, *MTX* methotrexate

[a]Dose indicated if reported

[b]Some studies reported time to onset in months, while others did not specify time in months and instead reported number of immune checkpoint inhibitor cycles

[c]Patient initially received two cycles of ipilimumab. Cutaneous sarcoid-like lesions were noted prior to pembrolizumab initiation, though 2 weeks after initiating pembrolizumab, granulomatous inflammation was noted in the lung

[d]Patient received 8 cycles of ipilimumab, followed by pembrolizumab for an unreported number of cycles

[e]Pulmonary SLGs were noted 4 months following treatment cessation. Neurosarcoidosis was noted 10 months following treatment cessation

[f]Patient required two oral corticosteroid tapers for non-SLG side effects—diarrhea and transaminitis—and two doses of infliximab 5 mg/kg for non-SLG immune-mediated colitis prior to immunosuppression administered for SLGs

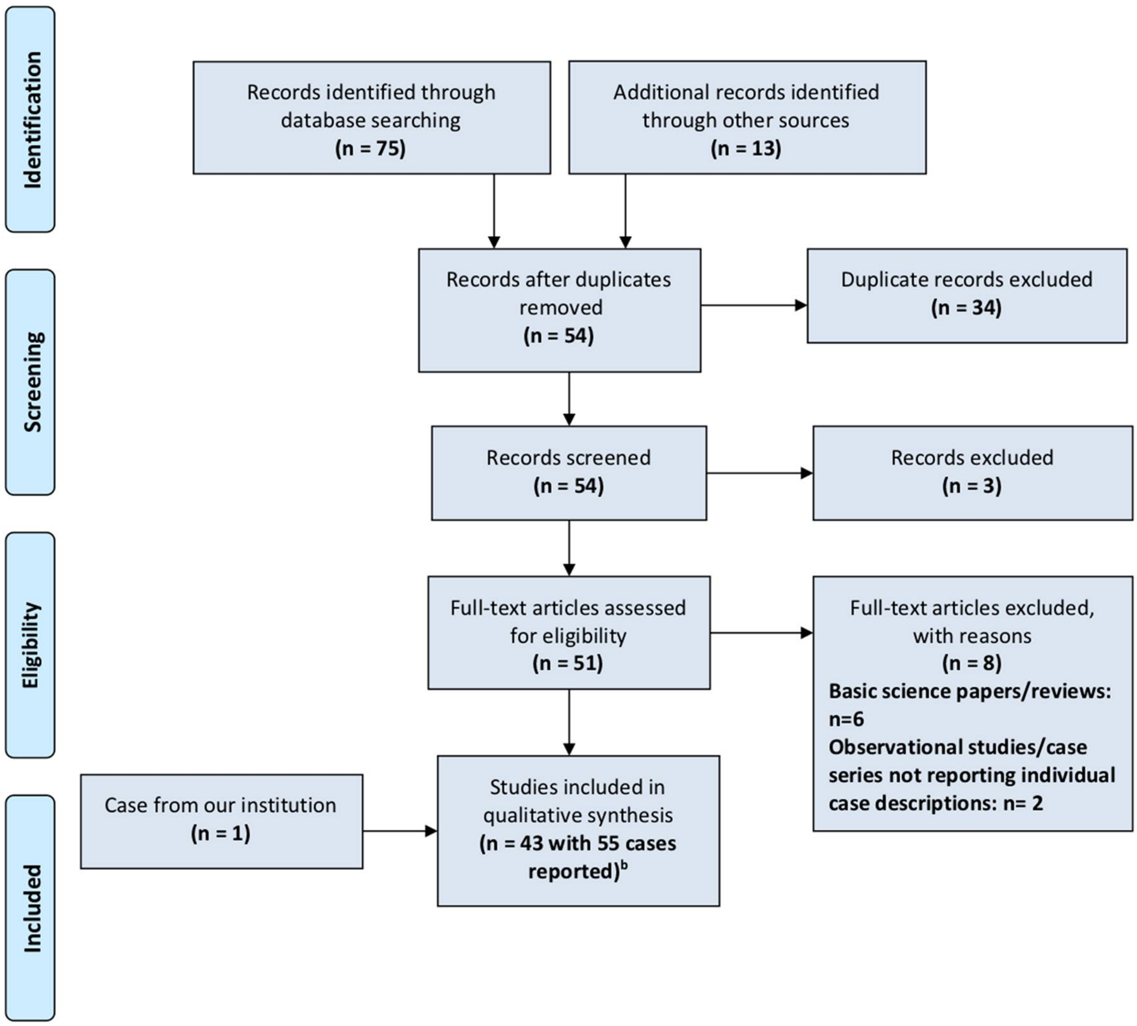

Fig. 1 PRISMA flowchart of selected immune checkpoint inhibitor studies for systematic review. [a]Search terms: ipilimumab induced sarcoidosis; pembrolizumab induced sarcoidosis; nivolumab induced sarcoidosis; ipilimumab and sarcoid like granulomas; pembrolizumab and sarcoid like granulomas; nivolumab and sarcoid like granulomas; immune checkpoint inhibitor sarcoid; pembrolizumab induced sarcoidosis like granulomas; PD-1 inhibitor and sarcoidosis; CTLA-4 inhibitor and sarcoidosis. [b]Cotliar et al. (2016) reported an additional two patients with similar histories as the case included in Table 2 but without biopsies to prove granulomatous inflammation. Both patients had resolution upon cessation of pembrolizumab. They were excluded from our systematic review due to lack of granular data (Clinical trial: NCT02406781) [24]

also drives the pro-inflammatory Th-1 and Th-17 immune responses and resultant T-cell proliferation in various tissues, including the lungs, spleen, and lymph nodes, as demonstrated through in vitro and in vivo murine studies [54]. Th-1- and Th-17-driven autoimmune conditions—psoriasis and thyroiditis—are common immune-related side effects of PD-1 inhibitors [55]. Taken together, these findings support the role of Th-1 and Th-17 cells in the development of iRAEs, especially SLGs in PD-1 inhibitor treated patients where the heightened Th-1/Th-17 immune response is the same cytokine milieu that favors sarcoidosis initiation.

In our search, patients with melanoma were those most frequently reported to have SLGs. While this is likely related to the earlier approval and increased use of checkpoint inhibitors for melanoma than for other cancer types, it is also possible that the substantial mutational burden of melanoma tumors potentiates iRAE development. The immunogenic nature of melanoma tumor neoantigens may result in an increased likelihood for melanoma patients to develop iRAEs when treated with checkpoint inhibitors [56–58]. Specifically, checkpoint inhibitors potentiate the anti-tumor response resulting in melanoma cell death, and in doing so, may further reveal tumor neoantigens. Once presented on host antigen-presenting cells, tumor neoantigens may fuel a Th-1 innate immune response, resulting in the pro-inflammatory cytokine environment that favors development of SLGs [40]. Additionally, studies have reported a higher incidence of

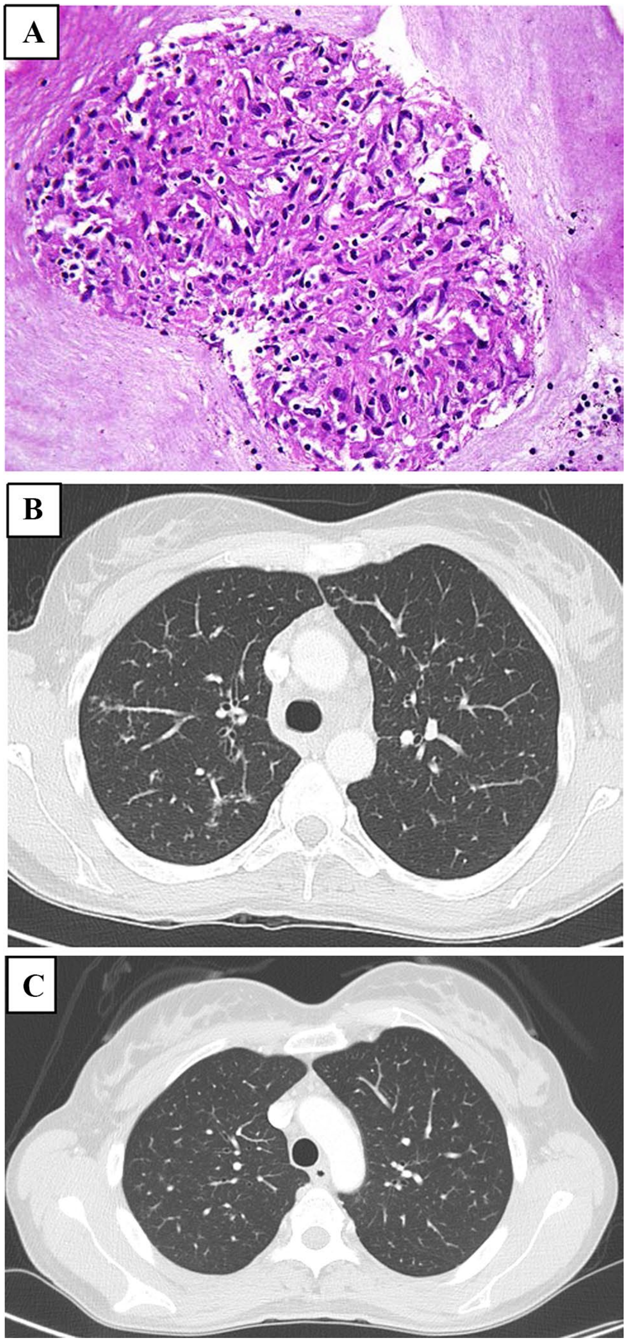

Fig. 2 Sarcoidosis-like granuloma in our melanoma patient on pembrolizumab. **a** Scanning magnification. Histopathology from needle biopsy of a hilar lymph node showing non-caseating granulomas. No malignant cells were identified. Mycobacterial and fungal organisms were not identified on acid fast and GMS ×200 magnification. **b** CT chest on pembrolizumab therapy. CT chest with oral contrast and intravenous Optiray 350, taken 8 months after the start of pembrolizumab, showing mediastinal and hilar lymphadenopathy as well as multiple, predominantly upper lobe, bilateral lung nodules, some in a tree-in-bud pattern, which had progressed in comparison to a CT scan performed 3 months prior. **c** CT chest after pembrolizumab cessation. CT chest with oral contrast and intravenous Optiray 350, taken 5 months after cessation of pembrolizumab, showing stable mediastinal and hilar lymph nodes and interval improvement of the pulmonary nodules

sarcoidosis in melanoma patients as compared to the general population, establishing a risk of sarcoidosis in these patients independent of checkpoint inhibitor therapy [59]. One study found increased levels of circulating Th-17 cells in melanoma patients prior to receiving PD-1 inhibitor therapy and at the onset of immunotherapy-related SLGs [33]. It is possible that the elevated circulating Th-17 cells in melanoma patients combined with the high mutational tumor burden set the stage for the formation of SLGs in the setting of immune checkpoint inhibitor therapy. Only one patient with SLGs had a reported history of asymptomatic pulmonary sarcoidosis prior to pembrolizumab treatment for Hodgkin lymphoma; that patient developed SLGs affecting the lungs, LN, bone, skin, and eyes [24].

In about one-fourth of SLG cases reported here, routine follow-up imaging revealed findings that were concerning for disease recurrence. Specifically, FDG PET/CT imaging done after ICI therapy can show enlarging hypermetabolic LNs. These radiological findings in conjunction with corresponding clinical signs and symptoms can pose a significant concern to the oncologist for disease progression. While other clinical data and findings may deem melanoma progression unlikely, such as presence of bilateral positive LNs, prompt biopsy is ultimately required to differentiate between SLG development and malignancy progression.

Use of CTLA-4 inhibition sequentially or concurrently with PD-1 inhibitors may increase the risk of SLGs. Of the total 55 cases reported here, 17 had sequential or concurrent ipilimumab and PD-1 inhibitor therapy. A recent single-center database study reported more iRAEs in patients treated with combination immune checkpoint inhibitor therapy compared to those receiving single-agent therapy [10]. Given that both PD-1 and CTLA-4 inhibitors independently promote Th-1/Th-17 hyperactive immune responses that can potentiate SLGs, combination or sequential therapy with these checkpoint inhibitors may synergistically increase the risk for sarcoid-like iRAEs.

Conclusion

In summary, sarcoidosis-like granulomatous inflammation is associated with immune checkpoint inhibitors, specifically CTLA-4 and PD-1 inhibitors, and is likely induced by a shift toward Th-1 and Th-17 immune pathway activation. Prompt investigation of potential SLGs in patients receiving immune checkpoint inhibitors is necessary to distinguish these from malignancy progression. As checkpoint inhibitors continue to show promising survival benefits in patients with various malignancies, early recognition and appropriate management of these side effects is crucial.

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Compliance with ethical standards

Conflict of interest Author PHR declares that she has no conflict of interest. Author BR declares that she has no conflict of interest. Author JFS declares that he has no conflict of interest. Author ANF declares that she has no conflict of interest. Author JAK declares that he has no conflict of interest. Author KH declares that he has no conflict of interest. Author HK owns stock in Company BMS. Author MRG has received research grants from the Char and Chuck Fowler Family Foundation.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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