Immune checkpoint inhibitors and the development of granulomatous reactions

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Immune checkpoint inhibitors (ICPIs) have emerged as a frontline treatment for a growing list of malignancies. Disruption of the negative regulatory immune checkpoints by ICPIs has been associated with many immune-related adverse events. Granulomatous reactions, such as sarcoidosis-like reactions, granulomatous panniculitis, granuloma annulare, and granulomatous dermatitis, are uncommon but increasingly recognized immune-related adverse events seen in patients treated with ICPIs. The frequency and significance of these eruptions, including whether they portend responsiveness to treatment, remain unclear. Additionally, understanding the role of immune checkpoint blockade in these reactions may provide mechanistic insight into the relevant signaling pathways involved in sarcoidosis and other granulomatous disorders. (J Am Acad Dermatol 2019;81:1165-75.)

Key words: checkpoint inhibitors; CTLA4; granuloma annulare; granulomatous; granulomatous dermatitis; granulomatous panniculitis; immune-related adverse events; PD-1; sarcoidosis.

Immune checkpoint inhibitors (ICPIs) have emerged as a frontline treatment for a growing list of malignancies. Currently, 2 classes of ICPIs have been approved by the US Food and Drug Administration for clinical use: (1) inhibitors of cytotoxic T-cell lymphocyte-associated protein 4 (CTLA4) and (2) inhibitors of either the programmed cell death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1). Disruption of the negative regulatory immune checkpoints by ICPIs has been associated with many immune-related adverse events (irAEs), such as autoimmune colitis, hepatitis, endocrinopathies, and various cutaneous eruptions, among others. Cutaneous toxicities in particular have a high incidence, ranging from 47% to 68% and 34% to 39% for anti-CTLA4 and anti–PD-1 agents, respectively.[1-4] These reactions include xerosis and pruritus, vitiligo (primarily in patients undergoing treatment for melanoma), autoimmune bullous diseases, and eruptions mimicking connective tissue disorders. With the increased use of ICPIs, many other rare irAEs have been reported, including a spectrum of granulomatous eruptions ranging from multiorgan sarcoidosis to granulomatous panniculitis to granuloma annulare (GA). The frequency and significance of these eruptions, including whether they portend responsiveness to treatment, remains unclear. Careful assessment and investigation of the immune response and cytokine profile of patients with granulomatous reactions (GRs) in the setting of ICPIs may provide insight into the development of

Abbreviations used:

CTLA4:	cytotoxic T-cell lymphocyte-associated protein 4
GA:	granuloma annulare
GD:	granulomatous dermatitis
GR:	granulomatous reaction
ICPI:	immune checkpoint inhibitor
irAE:	immune-related adverse events
PD-1:	programmed cell 1
PD-L1:	programmed death ligand 1
SLR:	sarcoidosis-like reaction
Th17 cell:	type 17 helper T cell

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sarcoidosis and other granulomatous conditions. In this article we review the growing number of ICPI-induced GRs in the literature and offer several potential pathophysiologic mechanisms for their development.

METHODS

Literature search

We performed a review of existing English-language literature on patients who developed GRs during or after ICPI therapy. The databases MEDLINE (1946-2018), Web of Science (1975-2018), Embase (1988-2018), and Scopus (1823-2018) were initially searched on December 17, 2017; a repeat search was conducted on June 14, 2018. Various terms and synonyms for *checkpoint inhibitors* and *granulomatous reactions* were used. A manual review of the references in the primary articles was performed to identify any additional articles potentially meeting the inclusion criteria. All article types reporting on 1 or multiple cases of ICPI GRs were included. Articles without histologic evidence to support the diagnosis of a granulomatous process were excluded. Patients undergoing combination immunotherapy with a non–checkpoint inhibitor were excluded.

CAPSULE SUMMARY

- Granulomatous reactions are an immune-related adverse event associated with immune checkpoint inhibitors.
- Sarcoidosis-like reactions can be misdiagnosed as metastatic disease progression and do not appear to be associated with a favorable tumor response.
- Cutaneous findings can facilitate timely and accurate diagnosis, avoiding unnecessary immunotherapy modifications.

Data extraction

The following parameters were documented: patient sex, patient age (at onset of GR), history of sarcoidosis or other granulomatous diseases, malignancy targeted by ICPI therapy, ICPI target (at the onset of GR), organ systems involved by the GR, symptoms and grade of severity (according to the Common Terminology Criteria for Adverse Events),[5] interval between initiation of current ICPI therapy to GR, GR treatment(s), tumor response, GR outcome, and other irAEs.

RESULTS

Study characteristics

The initial literature search yielded a total of 1133 articles. In 56 articles published between 2009 and 2018, there were 59 patients with sarcoid-like GRs (Table I[6-54]) and 13 patients with other GRs (Table II[28,55-62]) including granulomatous panniculitis (n = 4), GA (n = 4), granulomatous dermatitis (GD) (n = 4), and granulomatous foreign body reaction (n = 1).

ICPI-induced SLRs

The median age of patients with sarcoidosis-like reactions (SLRs) was 59 years (range, 26-83 years), with a slight female predominance (55.5% [30 of 59]). Most patients had a diagnosis of melanoma (81.4% [48 of 59]). Pre-existing sarcoidosis or other granulomatous pulmonary disease was rare (6.8% [4 of 59]). The majority of cases occurred in the setting of PD-1 (59.3% [35 of 59]) and CTLA4 (33.9% [20 of 59]) blockade, respectively, with rare cases due to either PD-L1 inhibition (1.8% [1 of 59]) or combined CTLA4 and PD-1 inhibitor therapy (5.1% [3 of 59]). The average delay between first ICPI dose and development of sarcoidosis-like lesions was 5.6 months (range, 0-24 months) or 5 doses, which was slightly higher that in the case of inhibitors of PD-1/PD-L1 (6.3 months; range, 0-24 months) or 6.2 doses (range, 1-27) compared with CTLA4 (4.8 months; range, 2 weeks-22 months) or 3.6 doses (range, 1-8). The earliest onset (3.5 months; range, 1.5-7 months) was seen in patients undergoing combination checkpoint inhibitor therapy. In a minority of patients (10.1% [6 of 59]), signs and symptoms of a SLR developed after ICPI therapy had been completed or discontinued.

Although the clinical presentation of SLRs is heterogeneous, pulmonary involvement is the most common manifestation (84.7% [50 of 59]) with cutaneous findings present in almost half (49.2% [29 of 59]) of cases. Skin findings include papules, plaques, and nodules, presenting on the head or face, trunk, or extremities and occasionally arising within tattoos or scars, which is typical of sarcoidosis. Pulmonary involvement is often asymptomatic, first being identified on routine radiographic imaging. Patients may experience mild symptoms of dry cough or dyspnea. Severe or life-threatening pulmonary involvement is uncommon and was reported in only 6.8% of patients (4 of 59) in this review. The average severity of pulmonary involvement was grade 2.4 (range, 1-4 [n = 7]). Grade for cutaneous or extrapulmonary involvement was not reported. Other irAEs were reported in 29% of patients

(17 of 59), with ophthalmologic issues and thyroiditis having the highest incidences.

In nearly all cases (94%) with a reported outcome of GR, the sarcoidosis-like lesions either improved or resolved completely. Systemic steroids were used in 57% of cases (29 of 51), ICPI therapy was interrupted or discontinued in 49% of cases (25 of 51), and minimal (eg, topical steroid) to no therapy was required in 24% (12 of 51). Where tumor response was reported, the percentage of patients who achieved a partial or complete response to immune checkpoint therapy (43% [15 of 35]) was slightly higher than the percentages of patients with progression of metastatic disease (37% [13 of 35]) or stable disease (20% [7 of 35]). Of the patients with progression of metastatic disease, 77% (10 of 13) received systemic steroids compared with 36% of patients with a partial or complete tumor response (5 of 14). Immunotherapy was interrupted or discontinued in 38% of patients (5 of 13) with progression of metastatic disease and 36% of patients (5 of 14) with a partial or complete tumor response.

Other GRs induced by ICPIs

Other GRs occurring in the setting of ICPI therapy include granulomatous panniculitis, GA, GD, and granulomatous foreign body reaction (which was reported in a single patient who developed a GR reaction to injection of permanent dermal filler 25 years earlier) (Table II). ICPI-induced granulomatous panniculitis is manifested as tender subcutaneous nodules affecting various areas of the body, with prominent involvement of the lower extremities. Histopathology is notable for a mixed (lobular and septal) or predominantly lobular granulomatous panniculitis comprising a variably dense lymphohistiocytic infiltrate with admixed multinucleated giant cells and without evidence of vasculitis.

All patients with ICPI-induced GA had localized disease presenting as pink papules or annular plaques preferentially involving the extremities (Fig 1). ICPI-induced GA was not associated with other systemic abnormalities. GA lesions responded to topical and oral steroids, but they recurred after ICPI therapy had been restarted. Complete or near-complete resolution was seen after ICPI therapy had been completed. No patients required ICPI discontinuation, and a partial or complete tumor response to immunotherapy was seen in all cases with a reported tumor outcome.

ICPI-induced GD presented as coalescing papules and plaques mainly affecting the torso and/or extremities. Although this reaction is typically mild (grade 1 in 2 of 4 patients),[60] a grade 3 reaction was reported in 1 patient.[61] There is a wide range of onset for GD (2 days-277 weeks), with the majority of cases occurring within 3 weeks of receipt of immunotherapy.

Management of ICPI-related GRs

With respect to management of ICPI-related GRs, withdrawal of immunotherapy was not required in the majority of cases. Treatment with systemic steroids (ie, prednisone, 1-2 mg/kg/d, may occasionally be necessary, particularly in SLRs with prominent systemic involvement. Topical steroids can be effective for limited cutaneous involvement, and observation alone may be appropriate in asymptomatic patients. Though these reactions may resolve spontaneously or with minimal intervention, recurrence in patients receiving immunotherapy on a repeated basis over an extended interval is uncertain.

DISCUSSION

Various GRs, including SLRs, GA, GD, and granulomatous panniculitis are increasingly recognized irAEs of ICPI therapy. Although certain irAEs, such as vitiligo in patients with melanoma,[63-65] have been associated with favorable clinical outcomes, patients with SLRs appear to achieve a favorable outcome (or partial to complete response) or develop progression of metastatic disease in comparable numbers of cases. The development of immunotherapy-related GA was associated with a favorable response to therapy and cancer prognosis in a small subset of cases.[57] Although these findings may play a role in understanding therapeutic response and development of granulomatous disease, establishing a clear association between GRs and ICPI efficacy is difficult given the small number of cases with a reported tumor response. Additionally, other factors, such as withdrawal of ICPI therapy or use of immunomodulatory agents to treat the GR, may influence clinical outcome. Although retrospective analyses have suggested that use of steroids for the management of irAEs is not associated with reduced ICPI efficacy, this is not clear owing to several confounding variables.[66,67] Larger, collaborative, multisite efforts and postmarketing surveillance will be required to accurately capture these rare events and establish their clinical and prognostic significance.

Sarcoidosis-like lesions are the most commonly reported immunotherapy-related GRs. Skin involvement was present in slightly less than half of patients with this reaction versus in 25% to 30% of those with typical sarcoidosis.[68,69] If we assume that these conditions have similar clinical characteristics, this discordance suggests the possibility that there may be under-recognition of SLRs that do not have skin

Table I. Sarcoidosis-like/non-necrotizing GRs

Pt No.	Sex/Age, y	Malignancy	ICPI target (at GR onset)	Time to GR (doses)	Treatment	Tumor response	GR outcome	Other irAE
Cutaneous only (n = 4)								
1[6]	F/60	Lung adenoCa	CTLA4 + PD-1	7 mo (3 doses of CTLA4; 10 doses of PD-1)	Topical steroids	PD	Improvement	Insulin-dependent diabetes, morbilliform eruption
2[7]	F/63	Lung adenoCa	PD-1	3.5 mo (7)	ICPI held, systemic steroids, hydroxychloroquine	SD	Resolution	
3[8]	F/56	Melanoma	PD-1	4 mo	NR	NR	NR	Thyroiditis
4[9]	M/72	Melanoma	PD-1	22 mo	None	SD	Not resolved	
Cutaneous and pulmonary (n = 25)								
5[10]	M/52	Urothelial carcinoma	CTLA4 + PD-1	2 mo	ICPI d/c'd (for PD), systemic steroids, hydroxychloroquine	PD	Improvement	
6[11]*	F/72	Hodgkin lymphoma	PD-1	6 mo	ICPI d/c'd, systemic steroid	CR	Resolution	Iritis
7[12]	F/44	Melanoma	CTLA4	3 mo (4)	None	CR	Resolution (skin), improvement (pulmonary)	
8[12]	M/81	Melanoma	PD-1	20 mo (27)	ICPI d/c'd, intralesional steroids	CR	Stable	
9[13]	F/71	Melanoma	PD-1	10.5 mo (8)	None	NR	Resolution	Uveitis
10[14]	F/75	Melanoma	PD-1	4 wk (2)	ICPI d/c'd, systemic steroids	NR	Improvement	Thyroiditis
11[15]	M/54	Melanoma	CTLA4	NR (2)	Systemic steroids	NR	Improvement	
12[16]	F/57	Melanoma	CTLA4	11 mo (6)	ICPI held, systemic steroids	SD	Resolution	Hepatitis
13[16]	F/55	Melanoma	CTLA4 + PD-1	6 wk (3)	ICPI held, systemic steroids	NR	Improvement	
14[17]	F/26	Melanoma	CTLA4	2 mo (2)	ICPI held, systemic steroids	PD	Improvement	Uveitis (posterior)
15[18]	F/83	Melanoma	PD-1	11 mo (8)†	None	PD	Resolution	Uveitis (anterior)
16[19]	F/42	Melanoma	PD-1	4.5 mo (6)	ICPI d/c'd	NR	Resolution	
17[19]	F/65	Melanoma	CTLA4	6 wk (2)	ICPI d/c'd, systemic steroids	NR	NR	
18[20]	M/60	Melanoma	PD-1	10 mo	None	CR	Resolution	
19[21]	F/46	Melanoma	CTLA4	NR (4)†	ICPI d/c'd (for PD), steroids (topical + systemic)	PD	Resolution	
20[22]	M/57	Melanoma	CTLA4	8 mo (6)†	ICPI d/c'd	SD	Resolution	
21[23,24]	F/67	Melanoma	CTLA4	7 mo (8)	ICPI d/c'd	SD	Improvement	
22[25]	M/55	Melanoma	CTLA4	6 wk (2)	Systemic steroids	PD	Resolution	
23[14]	F/62	Melanoma	PD-1	2 mo (3)	ICPI held	NR	Improvement	
24[26]	F/69	Melanoma	PD-1	1 mo.	NR	NR	NR	
25[27]	F/57	Melanoma	PD-1	7 mo	ICPI held, systemic steroids	CR	Resolution	
26[9]	M/65	Melanoma	PD-1	1 mo. (4)	Steroids (systemic + topical)	PD	Resolution	
27[9]	M/61	Melanoma	PD-1	3 mo	Topical steroids	CR	Resolution	Thyroiditis
28[28]	F/69	Melanoma	PD-1	NR (6)	ICPI held, systemic steroids	CR	Resolution	Granulomatous panniculitis
29[29]	F/56	NSCLC	PD-1	NR (5)	ICPI d/c'd	PR	Resolution	

Pulmonary and/or extrapulmonary without cutaneous involvement (n = 30)								
30[30]	M/55	Melanoma	CTLA4	22 mo (4)†	None	SD	Resolution	
31[31]	M/76	Melanoma	PD-L1	NR	ICPI d/c'd	NR	Resolution	
32[12]	M/69	Melanoma	PD-1	6 mo (9)	None	CR	Resolution	
33[32]	NR/NR	Melanoma	PD-1	NR	Systemic steroids	NR	Resolution	
34[32]	NR/NR	Melanoma	PD-1	NR	NR	NR	NR	
35[32]	NR/NR	Melanoma	PD-1	NR	NR	NR	NR	
36[33]	M/67	Melanoma	PD-1	2 mo	Systemic steroids	CR	Resolution	
37[14]	M/45	Melanoma	PD-1	2 mo	Systemic steroids	NR	Stable	Colitis
38[34]*	F/47	Melanoma	PD-1	1.4 wk (1)	ICPI held, systemic steroids	PD	Improvement	
39[35]	F/54	Melanoma	PD-1	24 mos.†	Systemic steroids	CR	Resolution	Pneumonitis (grade 3), fatigue (grade 2)
40[36]*	F/65	Melanoma	PD-1	12 mos.†	Systemic steroids	NR	Improvement	
41[37]	F/57	Melanoma	CTLA4	NR	ICPI d/c'd	NR	Resolution	Thyroiditis, inflammatory arthritis
42[38]	F/36	Melanoma	PD-1	5 mo	ICPI d/c'd	NR	Improvement	
43[39]	F/56	Melanoma	CTLA4	4 wk (2)	ICPI d/c'd, systemic steroids	PD	Resolution	Arthralgias (grade 1)
44[40]	M/37	Melanoma	CTLA4	4 mo (4)	Systemic steroids	SD	Resolution	
45[41]	M/66	Melanoma	CTLA4	3 mo (4)	Systemic steroids	PD	Resolution	
46[42]	M/63	Melanoma	CTLA4	4 mo (4)	None	CR	Resolution	Nausea (grade 1)
47[43]	M/61	Melanoma	PD-1	3 wk (2)	Systemic steroids	PD	Resolution	Dry eye
48[13]	M/61	Gallbladder adenoCa	PD-1	0 d (1)	Systemic steroids	NR	Improvement	Rash
49[44]	NR/NR	Prostate cancer	CTLA4	3 mo (3)	ICPI d/c'd, systemic steroids	NR	Resolution	
50[45]	F/58	Uterine LMS	PD-1	6 wk (2)	ICPI d/c'd	NR	Resolution	
51[46]	M/74	NSCLC	PD-1	4 mo (6)	NR	PR	NR	
52[47]	F/35	Melanoma	PD-1	NR	None	PD	NR	
53[48]	M/64	Melanoma	CTLA4	4 mo	NR	NR	Resolution	
54[49]*	M/NR	Melanoma	CTLA4	2 wk (1)	Systemic steroids	PD	Improvement	Myalgias (grade 3)
55[50]	F/42	Melanoma	CTLA4	NR	Systemic steroids	NR	Resolution	
56[51]	M/65	Melanoma	CTLA4	3 mo (4)	ICPI d/c'd, systemic steroids	NR	Resolution	
57[52]	M/70	NSCLC	PD-1	3 mo (8)	None	PR	Stable	
58[53]	F/64	RCC	PD-1	10 mo	NR	NR	Resolution	
59[54]	NR/NR	Melanoma	PD-1	NR	NR	NR	NR	

adenoCa, Adenocarcinoma; *CR*, complete response; *CTLA4*, cytotoxic T-cell lymphocyte-associated protein 4; *d/c'd*, discontinued; *F*, female; *GR*, granulomatous reaction; *ICPI*, immune checkpoint inhibitor; *irAE*, immune-related adverse event; *LMS*, leiomyosarcoma; *M*, male; *NR*, not reported; *NSCLC*, non–small cell lung carcinoma; *PD*, progressive disease; *PD-1*, programmed cell death 1; *PD-L1*, programmed death ligand; *PR*, partial response; *Pt*, patient; *RCC*, renal cell carcinoma; *SD*, stable disease.

*History of sarcoidosis.

†GR developed after completion or discontinuation of ICPI therapy.

Table II. Other GRs

Pt. no.	Sex/age (y)	Malignancy	ICPI target (at GR onset)	Time to GR (doses)	Treatment	Tumor response	GR outcome	Other irAE
Granulomatous panniculitis (n = 4)								
1[55]	M/70	Melanoma	PD-1	7 mo	ICPI d/c'd, systemic steroids	NR	Near-complete resolution	
2[28]	F/69	Melanoma	PD-1	5 wk (2)	ICPI held, systemic steroids	CR	Resolution within 15 d	SLR (hilar and mediastinal adenopathy; granulomatous nevus regression)
3[56]	F/57	Ovarian carcinoma	CTLA4 + PD-1	10 mo	None	PD	Resolution 4 mo after ICPI d/c'd (for PD and pneumonitis)	Pneumonitis
4[56]	F/39	Melanoma	PD-1	3 mo	ICPI d/c'd, systemic steroids, hydroxychloroquine	CR	Improvement after 5 mo	
Granuloma annulare (n = 4)								
1[57]	F/74	Urothelial carcinoma	PD-1	2 mo (4)	Steroids (topical or systemic)	CR	Response to steroids, resolution after ICPI therapy completed	
2[57]	M/65	Tonsillar SCC	PD-L1	8 mo	Steroids (topical or systemic)	PR	Response to steroids	
3[57]	M/76	Melanoma	PD-1	6 mo	Steroids (topical or systemic)	CR	Response to steroids	Vitiligo
4[58]	M/29	Melanoma	CTLA4	6 wk (3)	None	NR	Near-complete resolution after ICPI therapy completed	
Granulomatous dermatitis (n = 4)								
1[59]	M/55	Melanoma	CTLA4	277 wk	ICPI d/c'd, systemic steroids, topical steroids	PR	Resolution within 13 wk	Acneiform eruption, morbilliform eruption, pruritus
2[60]	M/72	Melanoma	CTLA4	3 wk (2)	ICPI held, systemic steroids	PD	Resolution	
3[60]	M/58	Melanoma	PD-1	<3 wk (1)	NR	SD	NR	
4[61]	M/63	Glioblastoma	PD-1	2 d (1)	Systemic steroids	NR	Resolution within 1 wk	
Granulomatous foreign body reaction (n = 1)								
1[62]	F/63	Melanoma	CTLA4	NR (2)	Excision	NR	Resolution	

CR, Complete response; *CTLA4*, cytotoxic T-cell lymphocyte-associated protein 4; *d/c'd*, discontinued; *F*, female; *GR*, granulomatous reaction; *ICPI*, immune checkpoint inhibitor; *irAE*, immune-related adverse event; *NR*, not reported; *PD*, progressive disease; *PD-1*, programmed cell death 1; *PD-L1*, programmed death ligand; *PR*, partial response; *Pt*, patient; *SCC*, squamous cell carcinoma; *SD*, stable disease; *SLR*, sarcoidosis-like reaction.

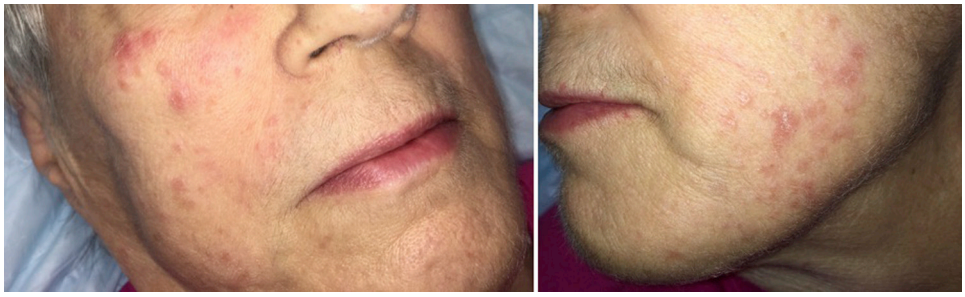

Fig 1. Immune checkpoint inhibitor–induced granuloma annulare in a patient with lung cancer. (Courtesy of Joseph English III, MD).

involvement. These reactions are often asymptomatic, being diagnosed only after abnormal findings are seen on routine radiographic imaging, which may contribute to their under-recognition. Importantly, the reactions can also radiographically mimic metastatic lesions, which may result in false diagnosis of progression of a patient's malignancy. In patient 20 (Table I), for example, ipilimumab therpay was discontinued after she received a diagnosis of presumed metastatic disease progression in the setting of increased size of the mediastinal masses and new and pulmonary parenchymatous micronodular lesions on CT imaging. This diagnosis was later changed to stable metastatic disease, and an immunotherapy-induced SLR after pathology from a newly formed skin lesion revealed noncaseating granulomas, prompting additional pulmonary testing, including bronchial biopsy.[23] This highlights the difficulty of diagnosing ICPI-induced GRs in the absence of cutaneous findings.

The majority of ICPI-related GRs, with the exception of GD, occurred several months after initiation of ICPI therapy, with few cases having delayed onset months after ICPIs had been discontinued. This is in line with other irAEs, which typically start in the first few weeks to months after initiation of therapy but can occur at any time, even after discontinuation of treatment. As with other irAEs, why GRs occur in only certain patients is not known. Only 4 patients with SLRs had a disease diagnosed as sarcoidosis or some other granulomatous lung condition at least 10 years earlier, and only 1 of those patients ever required treatment for the disease.[11,34,36,49]

The precise pathophysiologic mechanism behind granuloma formation in the context of immune checkpoint inhibition is not fully understood. Although antitumor granuloma formation in the setting of ipilimumab therapy for melanoma has been reported, this is likely a distinct irAE and unrelated clinically to other types of ICPI-related GRs.[70] In SLRs, the pathologic findings are similar to those seen in sarcoidosis, with notably absent malignant cells and negative immunohistochemistry findings for protein S100, melanoma antigen recognized by T cells, and melan-A in patients with melanoma. Infectious causes of granulomas, particularly reactivation of mycobacterial granulomas, should be excluded by special stains and/or tissue culture.

Moreover, the immunopathologic mechanisms of sarcoidosis, a granulomatous condition that is thought to be the result of an uncontrolled cell-mediated immune reaction, are also not fully understood.[71] There is evidence for activation of the innate immune system, dysfunction of regulatory T cells, and expansion of type 17 helper T (Th17) cells, Th17.1 cells, and C-C motif chemokine receptor 6–positive double-positive cells, which are thought to reflect an intermediate stage between Th17 and Th17.1 cells.[72-76] The primary Th17 and Th17.1-cytokines, interleukin 17a and interferon gamma, respectively, are essential in granuloma formation and multinucleated giant cell fusion.[77-80] Reduced coinhibitory CTLA4 expression has been observed in Th17 cells and C-C motif chemokine receptor 6–positive double-positive cells in sarcoidosis, likely contributing to increased proliferative capacity.[81,82] Disturbances in T-cell costimulation are also suspected to be involved in the pathogenesis of sarcoidosis, as evidenced by development of granulomatous disease in the setting of mutated butyrophilin-like 2, a B7 family member that is thought to function as a negative costimulatory molecule.[74,75,83,84] ICPIs may potentially promote granuloma formation through 1 or more of these mechanisms.

Immunotherapy-related GRs may be triggered by a checkpoint inhibitor–mediated Th17 immune response. CTLA4 inhibitors have been associated with expansion of Th17 cells in patients with SLRs,[42,85] which may lead to granuloma formation through Th17-related cytokines. Regulatory T-cell/Th17 balance is also regulated by the PD-1/PD-L1 pathway. Blockade of PD-1/PD-L1 has been

associated with Th17 cell hyperactivity and increased interleukin 17 expression.[86,87] Abnormally high numbers of circulating Th17.1 cells have been reported in patients with melanoma before receipt of anti–PD-1 immunotherapy and onset of ICPI-induced SLR.[14] Although these findings may support the existing literature stating that Th17.1 cells are involved in the pathogenesis of sarcoidosis, the strength of the authors' conclusions is limited by the presence of elevated baseline levels of Th17.1 cells seen in a subset of patients with advanced melanoma who did not develop sarcoidosis. Blockade of the PD-1/PD-L1 pathway also results in increased phosphatidylinositol 3-kinase–protein kinase B mechanistic target of rapamycin (mTOR) expression.[88,89] Constitutive activation of the mTOR complex 1 pathway in macrophages has been shown to spontaneously induce the formation of granulomas.[90] Given these findings, ICPI blockade of the PD-1/PD-L1 pathway may promote the formation of granulomas through chronic activation of the mTOR pathway.

Despite evidence that PD-1/PD-L1 inhibitors can induce GRs that may resolve after discontinuation of immunotherapy, there are data to suggest that PD-1 blockade may restore normal immune function in patients with active sarcoidosis.[88,91,92] Recent studies investigating the PD-1 pathway in sarcoidosis have demonstrated upregulation of PD-1 and PD-L1 expression and subsequent reduced $CD4^+$ T-cell proliferative capacity, during disease progression and reduced PD-1 expression, with restored T-cell function and spontaneous clinical resolution following PD-1 pathway blockade.[88,89,93] These findings highlight the overall complexity of checkpoint inhibition in the maintenance of immune homeostasis and the need for further research in this area.

This review is limited by the quality of the data available in the reports, which largely include case reports and abstracts, given the rarity of this adverse event. Additionally, case reports of adverse events are likely to report unique, unusual, or severe features, which may lead to a potential publication bias. This also limits the ability to infer overall frequency or severity of these reactions.

CONCLUSION

GRs are becoming an increasingly recognized irAE associated with the use of checkpoint inhibitors. Cases with systemic involvement may easily be mistaken for metastatic disease progression. Therefore, clinicians must maintain a high degree of suspicion for these reactions to avoid misdiagnosis and unnecessary immunotherapy modifications. Cutaneous findings, when present, can facilitate timely and accurate diagnosis. Immune checkpoints play a complex role in granuloma pathogenesis and future studies are needed to better understand their immunologic and clinical significance. Understanding the role of immune checkpoint blockade in these reactions may provide additional mechanistic insight into the relevant signaling pathways involved in sarcoidosis and other granulomatous disorders.

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