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Sarcoid-like reactions in patients receiving modern melanoma treatment

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The development of cancer immunotherapy and targeted therapy has reached an important inflection point in the history of melanoma. Immune checkpoint inhibitors and kinase inhibitors are today's standard of care treatments in advanced melanoma patients. Treatment-related toxicities can be very intriguing and quite challenging. Sarcoidosis is a multisystemic granulomatous disease characterized by an aberrant immune response to unknown antigens, whereas sarcoid-like reactions (SLRs) refer to localized clinical features. We carried out a single-center observational study in patients with stage IIB–IV melanoma treated with BRAF/MEK inhibitors and immune checkpoint inhibitors. A description of the sarcoidosis-related manifestations was provided from patients' records. We observated eight cases of SLRs in a cohort of 200 patients. The clinical courses were characterized by a variety of symptoms, accompanied by cutaneous signs and extracutaneous manifestations such as bilateral, hilar lymphadenopathy. We identified a histologically granulomatous inflammation involving the skin, the lungs, and the lymph nodes. Two patients presented with cutaneous lesions only, and three patients had lung involvement only. Three patients achieved complete and partial response of the melanoma disease, and three patients had stable disease. Disease progression was documented in two patients. The reported immune-related adverse events were mild to severe and in most of the cases were continued without any treatment cessation. SLRs appear during treatment with both kinase and immune checkpoint inhibitors. Awareness of these can avoid misdiagnosis of disease progression and unnecessary treatment changes. ***Melanoma Res*** **28:230–236 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

The development of cancer immunotherapy and targeted therapy has reached an important inflection point in the history of melanoma. The immune checkpoint inhibitors, targeting either the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death protein 1 (PD-1) and its ligand (PD-L1), as well as treatment with the kinase inhibitors (BRAF and MEK inhibitors) are current standard of care in advanced melanoma [1,2]. However, the treatment-related toxicities can be quite challenging from the clinical, diagnostic, and therapeutic point of view [3–5]. Sarcoidosis is a multisystemic granulomatous disease characterized by an aberrant immune response to unknown antigens, initiated by T-helper 1 cells secreting interleukin-2 (IL-2) and interferon (IFN)-γ, leading to the activation of additional T cells and macrophages [6,7]. The diagnosis includes a typical clinical and radiological presentation, accompanied by histologically confirmed noncaseating granulomas and exclusion of alternative diseases. In addition to sarcoidosis, sarcoid-like reactions (SLRs), which refer to localized clinical features without fulfilling the sarcoidosis criteria, increasingly occur during modern melanoma therapy. Antineoplastic therapies, such as IFN, cisplatin, and IL-2, have been previously associated with the development of sarcoid-like reactions, mostly owing to the macrophage and T-cell modulation [8].

Methods

A single-center retrospective analysis of patients with stage IIB–IV melanoma (American Joint Committee on Cancer, AJCC, 7th ed.) treated with BRAF/MEK and immune checkpoint inhibitors was carried out in the Dermatology Department of the University Hospital of Zurich from January to May 2017 aiming to investigate

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the frequency and the clinical and histological features of SLRs in them. The patients were selected according to the clinical and radiological presentation of the disease, as well as the histological findings. Description of the clinical reactions was provided from patients' electronical medical records. Skin biopsies were examined by a board-certified dermatopathologist. Data were collected according to the approval of the ethics commission (EK no. 647/800) and following the guidelines of the Helsinki Declaration on Human Rights.

Results

In total, we identified eight of 200 patients with melanoma with a mean age of 56 years, who were at different clinical stages of melanoma (AJCC stage IIB–IV) at the onset of the SLR. Patients' characteristics are shown in Table 1. None of the patients had diabetes mellitus or arthritis before appearance of SLRs. Two patients had additionally received ipilimumab and BRAF/MEK inhibitors (vemurafenib and LGX818/MEK162, respectively) before the onset of the reaction (Table 1). These treatments are also known to be potential inducers of sarcoid-like immune reactions. During the onset of the SLR, three patients were treated with anti PD-1 antibody [pembrolizumab as monotherapy or as a combination with IDO-1/placebo within the keynote-252 study (NCT02752074)], two patients were under treatment with kinase inhibitors [dabrafenib/trametinib and LGX818/MEK162 within the logic-2 study (NCT02159066)], and one patient received nivolumab or ipilimumab [BMS 238 study (NCT02060188)]. However, two patients were diagnosed with SLRs before any systemic therapy.

Among the patients who were diagnosed with a SLR after treatment induction, the symptoms developed in a median time of 5 months (range: 1–22 months). In all patients, the reactions were characterized by a variety of cutaneous signs and extracutaneous manifestations. The radiological presentation was in five cases mediastinal and hilar lymphadenopathy and in one case bilateral lung lesions. Histological signs of skin sarcoidosis were either skin granulomas or erythema nodosum. In one patient, the diagnosis was suspected only radiologically. Evidence of noncaseating granulomas was found in three patients with lung and mediastinal lymph node involvement. Two patients presented only with cutaneous lesions and two patients had only systemic symptoms. All in all, patients 5 and 7 met the criteria for systemic sarcoidosis. In six of eight cases, the symptoms were mild to severe and resumed without treatment cessation. Two patients were treated with systemic steroids, 50 and 20 mg/daily for 2 weeks, with complete recovery.

The melanoma response was measured according to the RECIST 1.1. Three patients achieved complete response or partial response during treatment and three patients had a stable disease (SD). Two patients had a progressive disease (PD) and one patient died owing to fatal disease progression.

In this retrospective analysis, the prevalence of sarcoidosis and SLRs in a cohort of 200 patients with melanoma was 4%, both under kinase and immune checkpoint inhibitors.

Case 1

A 65-year-old male was diagnosed with AJCC (7th ed.) stage IIIC melanoma of the right scapula region in 2016 (initial Breslow tumor thickness 2.6 mm, with ulceration). Following surgical removal of the primary tumor, a regional lymphadenectomy was performed, which identified additional nodal micrometastasis (1/9) and skin satellite-metastases (pN3). A PET-computed tomography (CT) manifested multiple other lymph node metastases and muscle metastases. Subsequently, he was enrolled in the randomized, double-blind, phase 3 keynote-252 clinical study (NCT02752074) of pembrolizumab in combination with epacadostat (IDO inhibitor) or placebo and had the first infusion of pembrolizumab administered in December 2016. After completing the fourth cycle of the therapy, he presented with reduced performance status, dry cough, and B-symptoms. The clinical examination revealed multiple subcutaneous nodules on the left elbow, without any other skin symptoms (Fig. 1a). A biopsy of the left elbow lesions showed granulomas infiltrates in the upper dermis (Fig. 1b), and specific staining results for pathogens (Ziehl–Neelsen and Brown–Brenn staining) were negative. CT scan of the lungs confirmed bilateral enlargement of the hilar lymph nodes without pulmonary parenchymal involvement, which was not previously reported. Blood chemistry and complete blood count were normal, aside from a mild anemia and increased levels of sIL-2R. Angiotensin-converting enzyme levels were measured and were normal (44.2 U/l, $N < 68$). Quantiferon test (a IFN-γ release test for *Mycobacterium tuberculosis*) result was shown to be positive, even though previous exposure to *M. tuberculosis* was unknown. The transbronchial biopsy of a mediastinal lymph node diagnosed noncaseating epitheloid granulomas surrounded by lymphocytes, typical for sarcoid granulomas. Bronchoalveolar lavage revealed an increase of the lymphocytes portion by 33% with a CD4/CD8 quotient of 3.6. Both PCR and microscopy findings were negative for *M. tuberculosis*. Furthermore, both blood and tissue culture findings were negative for mycobacteria and other pathogens. Other infections ending in granulomatous inflammation were unlikely owing to the clinical symptoms.

Taking these findings into account, the diagnosis of sarcoidosis induced by pembrolizumab was suggested. The patient received systemic corticosteroids (prednisolone 20 mg/day for 12 days), and the symptoms resolved fully within 2 weeks not requiring withdrawal from the study. However, the patient stopped the treatment in March 2017 owing to fatal disease progression.

Case 2

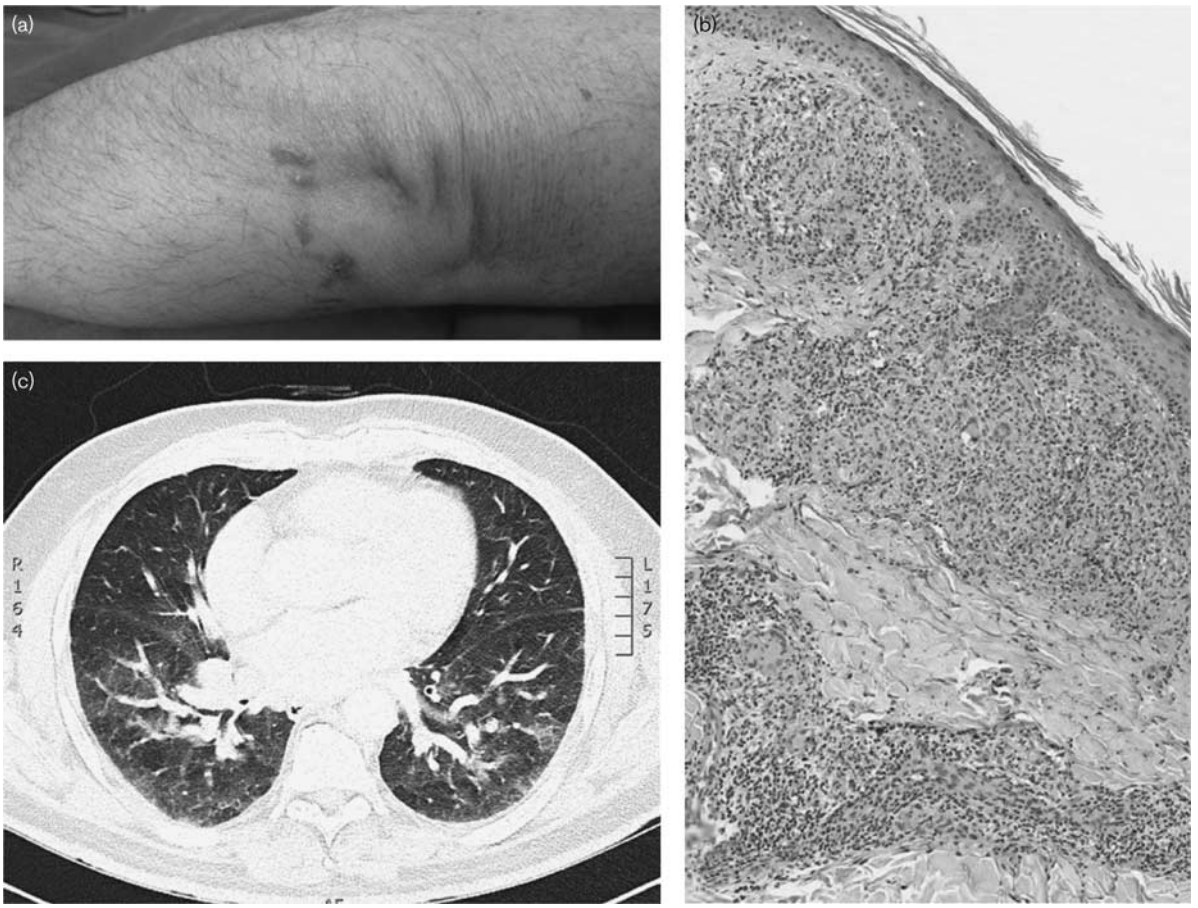
A 57-year-old male was diagnosed with AJCC (7th ed.) stage IIIB melanoma of the right lower leg in 2011 (initial

Table 1 **Cases of sarcoid-like reactions: features of patients' characteristics, melanoma diagnosis and treatment as well as clinical and histological features of sarkoid-like reactions**

Age	American Joint Committee on Cancer (7th ed.) stage	Previous treatment for melanoma	Treatment by onset of sarcoid-like immune reaction	Duration of treatment before onset of sarcoidosis	Cutaneous symptoms	Radiological presentation	Histological documentation	Treatment	Outcome of sarcoidosis	Treatment cessation	Melanoma response
73 (male)	IV (M1a)	Vemurafenib, ipilimumab, and LGX818/ MEK162 (logic-2 study, NCT02159066)	Pembrolizumab	15 months	None	Mediastinal and hilar lymphadenopathy	–	None	Not recovered/ not resolved	No	CR
76 (male)	IIB	None	None	–	None	Mediastinal and hilar lymphadenopathy	Noncaseating granuloma (mediastinal lymph nodes)	None	Remission	–	PD
19 (male)	IV (M1c)	None	Dabrafenib/trametinib	1 month	Subcutaneous nodules	None	Erythema nodosum (skin)	Topical corticosteroids	Remission	No	CR
72 (male)	IV (M1c)	Ipilimumab	Pembrolizumab	22 months	Subcutaneous nodules	None	Skin granuloma (skin)	None	Not recovered/ not resolved	No	SD
33 (male)	IV (M1b)	None	LGX818/MEK162 (logic-2 study, NCT02159066)	4 months for cutaneous disease, and 21 months for pulmonary disease	Subcutaneous nodules	Bilateral lung lesions	Noncaseating granuloma (lower left lung) Erythema nodosum (skin)	Systemic and topical corticosteroids	Remission	No	PR
57 (male)	IIIB	None	Ipilimumab vs. nivolumab (BMS 238 study, NCT02060188)	3 months	Erythematous papules in old scars	Mediastinal and hilar lymphadenopathy	Skin granuloma (skin)	Topical corticosteroids	Remission	No	SD
65 (male)	IV	None	Pembrolizumab and epacadostat/ placebo (keynote-252 study, NCT02752074)	1 month	Subcutaneous nodules	Mediastinal and hilar lymphadenopathy	Noncaseating granuloma (mediastinal lymph nodes) Skin granuloma (skin)	Systemic and topical corticosteroids	Remission	No	PD and death
59 (male)	IIB	None	None	–	None	Mediastinal and hilar lymphadenopathy	Lipogranulomatosis (axillary lymph nodes)	None	Not recovered/ not resolved	–	SD

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Fig. 1



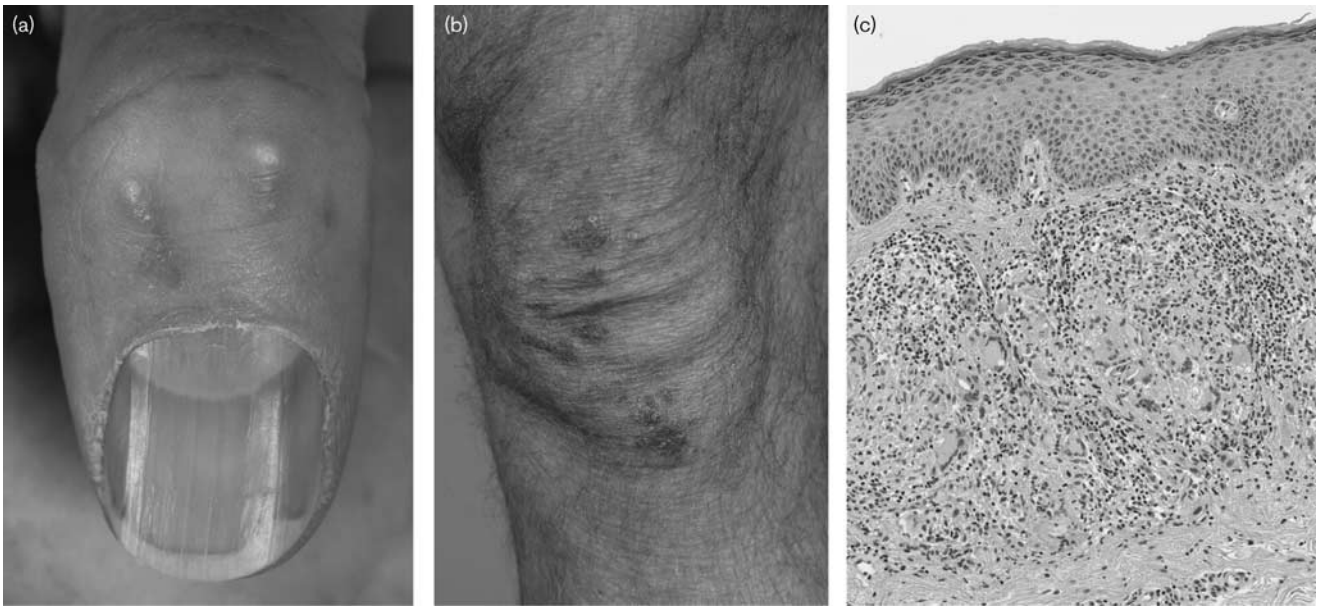
(a) Cutaneous sarcoidosis lesions on the left elbow with erythematous papules. (b) Histopathological characteristics with HES staining. Biopsy of the site shown in (a) showed granulomas infiltrates. (c) Computed tomography scan showing enlarged bilateral, hilar lymph nodes.

depth 1.1 mm, no ulceration), with satellite metastases without metastatic nodes. He had two local recurrences in 2013 and 2014, both followed by resection. In 2015, he underwent a new surgery owing to a third local recurrence, and afterward, he was included in an adjuvant trial of nivolumab versus ipilimumab (NCT02060188). The study drugs were well tolerated apart from the development of an autoimmune thyroiditis requiring replacement therapy. In December 2015, the patient presented with erythematous papules in all his old scars at the left thumb, knee, thigh, and lower leg (Fig. 2a and b). Skin biopsy showed sarcoid-like granulomatous infiltration in the upper dermis, a so-called scar sarcoidosis (Fig. 2b). PET-CT scan revealed multiple enlarged mediastinal lymph nodes with FDG-positive activity. The skin lesions were treated successfully with topical class III steroids (mometasone furoate). The hilar lymphadenopathy regressed spontaneously after 6 months. The melanoma is still in complete regression (08/2017), and the patient has no flare-up of granulomatous reactions.

Discussion

Sarcoidosis is a systemic inflammatory disease of unknown etiology characterized by the formation of noncaseating granulomas in multiple organ systems. The development of this disorder is defined by an extended type 1 helper-like cells (Th1) immune response, which is primarily inducted by the presence of CD4 + Th1 cells, which interact with antigen-presenting cells and initiate the formation and maintenance of centrally organized collections of epitheloid histiocytes and macrophages surrounded by giant cells and lymphocytes (non-necrotizing granulomas). Activated CD4 + T-cells differentiate into Th1, thus leading to IL-2 and INF-γ secretion and secondarily tumor necrosis factor (TNF-α) production, through the activation of antigen-presenting macrophages [6,7]. This chronic cytokine stimulation consists of pleomorphic manifestations, affecting various organs, mainly the lungs, the lymph nodes, and the skin. The clinical spectrum of the disease often includes systemic symptoms, such as fatigue, night sweats, and weight loss, as well as pulmonary and extrapulmonary signs.

Fig. 2



(a, b) Multiple, erythematous papules in old scars of the left thumb and lower leg (scar-sarcoidosis). (c) Histopathological features: granulomatous infiltration in the upper dermis.

The association between sarcoidosis and malignant disease has been discussed controversially in the literature [8,9]. Hematologic malignancies and solid tumors, including melanoma, have been associated with sarcoidosis and vice versa; previous data seem to describe a possibility of an increased incidence of malignancies in patients with sarcoidosis, although an etiological correlation is not known [10]. Sarcoidosis may present before, during, or after the diagnosis of cancer. Moreover, therapy of the malignancy can either induce or flare a sarcoidosis.

Most of the reported cases of SLRs in patients with melanoma have been associated with immunotherapy (Table 2). Although immune checkpoint inhibitors targeting CTLA-4 and PD-1 or its ligand (PD-L1) are able to provide durable responses and significant survival benefit in advanced melanoma [27–29], many patients will often develop manifestations of autoimmunity (irAEs) [3,4] such as colitis and pneumonitis [30]. It has been previously shown that the CTLA-4 blockade results in an increase in Th17 CD4+ cells in peripheral blood, thus leading to an extended production of proinflammatory molecules, such as IL-6 and TNF-α [18]. IL-2 secretion by activated T cells is besides assumed to be involved in the pathogenesis of sarcoidosis [31]. Recently, it was shown that PD-1 pathway is upregulated in sarcoidosis [32]. Even though sarcoidal PD-1+CD4+T cells display reduced proliferation rate, their proliferation capacity can recover after treatment with anti-PD-1, suggesting a potential benefit and a dual role of PD-1 blockade in sarcoidosis, similar to TNF-α blockers [32].

Table 2 Case reports of sarcoid-like granulomatous reactions in selected studies induced by immunotherapy and targeted therapy in patients with melanoma

References	Melanoma treatment
Adam *et al.* [11]	Vemurafenib
Lheure *et al.* [12]	Vemurafenib
Park *et al.* [13]	Vemurafenib and dabrafenib
Green *et al.* [14]	Dabrafenib and trametinib
Moessner *et al.* [15]	Vemurafenib and dabrafenib, and trametinib
Seve *et al.* [9]	Ipilimumab
Eckert *et al.* [16]	Ipilimumab
Tissot *et al.* [17]	Ipilimumab
Vogel *et al.* [18]	Ipilimumab
Berthod *et al.* [19]	Ipilimumab
Reule and North [20]	Ipilimumab
Wilgenhof *et al.* [21]	Ipilimumab
Murphy *et al.* [22]	Ipilimumab
Andersen *et al.* [23]	Ipilimumab
Danlos *et al.* [24]	Nivolumab
Koelzer *et al.* [25]	Ipilimumab and nivolumab
Reuss *et al.* [26]	Ipilimumab and nivolumab

On the contrary, BRAF and MEK inhibitors have been reported to induce a variety of dermatological toxic effects, including granulomatous eruptions, panniculitis, and erythema nodosum-like lesions [11,12,15,33,34]. Although the development of SLRs seems to be a paradoxical adverse event of the BRAF/MEK inhibitors, recent data confirm their immunomodulatory effect on the tumor microenvironment. The inhibition of the MAPK pathway has been associated with increased CD8+T-cell infiltration and PD-L1 expression [35]. The pathogenesis of the SLRs could be moreover explained by the increased levels of TNF-α and IFN-γ, which can induce the granuloma formation [12].

In most of the cases, the SLR presented mostly a benign, uncomplicated disease. The cutaneous sarcoidal manifestations can be treated with potent topical steroids, as in the majority of our cases, thereby preventing an immune therapy discontinuation [13]. Spontaneous resolution of the skin lesions has also been reported. However, patients with severe systemic involvement may require corticosteroids or other immunosuppressants for symptomatic relief, although these agents might have a negative effect on the efficacy of the melanoma treatment.

Conclusion

Our observations indicate that SLRs can appear both under kinase and immune checkpoint inhibitors, suggesting an immune response against melanoma as one possible causative event in granuloma formation. Awareness of sarcoidal reactions and their radiologic features can avoid misdiagnosis of disease progression and unnecessary treatment changes, thus suggesting the elimination of metastatic disease and the complete evaluation of the symptoms as crucial.

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Conflicts of interest

R.D. has intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, and Pierre Fabre outside the submitted work. S.M.G. receives travel grant support and is an intermittent board advisory member for Bristol Myers Squibb, Merck, Novartis, and Roche and receives research funding from the University of Zurich. J.M. has temporary advisory relationship and receives travel support from MSD and Merck. M.U.-M. has received honoraria from Bristol-Myers Squib, Novartis, Amgen, and Roche. F.D., A.F., J.K., D.F., R.B., M.C.N., and M.B. have declared no conflicts of interest.

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