CASE REPORTS

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Sarcoidosis-like reaction induced by immune checkpoint inhibitors in patients with advanced melanoma: a report of two cases and a brief review of the literature

Reakcija slična sarkoidozi izazvana inhibitorima kontrolnih tačaka kod bolesnika sa uznapredovalim melanomom: prikaz dva slučaja i kratak pregled literature

Branko Dujović*†, Lidija Kandolf*†, Tatjana Radević*†, Nenad Petrov‡, Željko Mijušković*†

Military Medical Academy, *Department of Dermatology and Venereology, ‡Center of Pathology and Forensic Medicine, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

Abstract

Introduction. Immunotherapy is associated with a wide range of adverse events. A drug-induced sarcoidosis-like reaction is a systemic granulomatous reaction that is no different from sarcoidosis and occurs in a certain temporal relationship with the initiation of the drug. **Case report.** The first presented patient was a 61-year-old male with stage IIIC BRAF-positive melanoma treated with adjuvant nivolumab therapy. After four cycles of therapy, enlarged mediastinal lymph nodes were confirmed using computed tomography. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy showed chronic granulomatous inflammation. After 12 cycles, grouped brownish-red papules and plaques covered with whitish scales were observed in the skin of both knees, and a histopathology finding indicated a sarcoidosis-like reaction. He was treated with oral prednisone, 60 mg daily in decreasing doses, and after 16 months, the enlarged mediastinal lymph nodes and skin lesions disappeared completely. The second presented patient was a 45-year-old male with stage IIIC BRAF-positive melanoma treated with adjuvant pembrolizumab therapy. After four cycles, enlarged mediastinal lymph nodes were observed. Bronchoscopy with bronchoalveolar lavage revealed granulomatous inflammation, and transbronchial biopsy confirmed sarcoidosis. Therapy with oral prednisone 40 mg daily in decreasing doses was performed in the next three months, and immunotherapy was continued. The enlarged mediastinal lymph nodes resolved after completion of adjuvant therapy. **Conclusion.** In most cases, a diagnosis of a sarcoidosis-like reaction requires a biopsy of the suspected lesions. It is not usually necessary to stop immunotherapy, but sometimes standard corticosteroid therapy is indicated. An interdisciplinary approach is important to distinguish true disease progression from adverse drug reaction.

Key words:
biopsy; diagnosis, differential; disease progression; drug-related side effects and adverse reactions; melanoma; sarcoidosis.

Apstrakt

Uvod. Imunoterapija je povezana sa širokim spektrom neželjenih događaja. Reakcija slična sarkoidozi, izazvana lekom, je sistemska granulomatozna reakcija koja se ne razlikuje od sarkoidoze i vremenski je povezana sa uzimanjem leka kojim je izazvana. **Prikaz bolesnika.** Prvi prikazani bolesnik bio je muškarac star 61 godinu sa BRAF pozitivnim melanomom u IIIC stadijumu, lečen adjuvantnom terapijom nivolumabom. Posle četiri ciklusa terapije, primenom kompjuterizovane tomografije utvrđeni su uvećani medijastinalni limfni čvorovi. Bronhoskopijom sa bronhoalveolarnom lavažom i transbronhijalnom biopsijom viđena je hronična granulomatozna inflamacija. Posle 12 ciklusa, na koži oba kolena uočene su braonkasto-crvene papule i plakovi prekriveni beličastim ljuspama, a histopatološkim nalazom utvrđena je reakcija slična sarkoidozi. Lečen je prednizonom oralno, 60 mg dnevno u opadajućim dozama i posle 16 meseci je došlo do kompletnog nestanka uvećanih medijastinalnih limfnih čvorova i promena na koži. Drugi prikazani bolesnik bio je muškarac star 45 godina sa BRAF pozitivnim melanomom u IIIC stadijumu, lečen adjuvantnom terapijom pembrolizumabom. Posle četiri ciklusa, uočeno je uvećanje

Correspondence to: Branko Dujović, University of Defence, Faculty of Medicine, Military Medical Academy, Department of Dermatology, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: brankodujovic@yahoo.com

medijastinalnih limfnih čvorova. Bronhoskopijom sa bronhoalveolarnom lavažom otkriveno je granulomatozno zapaljenje, a transbronhijalnom biopsijom potvrđena je sarkoidoza. Terapija prednizonom oralno 40 mg dnevno u opadajućim dozama primenjivana je naredna tri meseca, a imunoterapija je nastavljena. Uvećani medijastinalni limfni čvorovi su se povukli posle završetka adjuvantne terapije. **Zaključak.** U većini slučajeva, za postavljanje dijagnoze reakcije slične sarkoidozi potrebna je biopsija sumnjivih lezija. Obično nije potrebno prekinuti imunoterapiju, ali je ponekad indikovana standardna terapija kortikosteroidima. Interdisciplinarni pristup je važan kako bi se razlikovala prava progresija bolesti od neželjene reakcije na lek.

Ključne reči:
biopsija; dijagnoza, diferencijalna; bolest, progresija; lekovi, neželjeni efekti i neželjene reakcije; melanom; sarkoidoza.

Introduction

Therapy with immune checkpoint inhibitors (ICIs) is associated with a wide spectrum of adverse events (AEs) related to their mechanism of action [1]. A drug-induced sarcoidosis-like reaction (DISR) is a systemic granulomatous reaction that is indistinguishable from sarcoidosis and occurs in a temporal relationship with the initiation of an offending drug [2]. Here, we report two cases of DSIR induced by adjuvant therapy of melanoma with ICIs.

Case report

Case 1

A 61-year-old man underwent melanoma excision from the skin of his right lower leg in October 2018. The histopathological (HP) findings were consistent with nodular melanoma: Breslow thickness 3.6 mm, Clark level IV with ulceration, and primary tumor (pT) defined as pT3b. In November 2018, a re-excision and sentinel lymph node biopsy (SLNB) was performed, and no metastasis was observed. In June 2019 and January and November 2020, excisions of satellite and in-transit metastases from the right lower leg were performed. Due to the presence of lymphadenopathy, evacuation of the right inguinal fossa was performed in December 2020, when metastasis in one lymph node had been confirmed on HP analysis. During that period, until January 2021, the patient did not receive any systemic therapy. BRAF testing from the primary tumor was performed, and a V600E mutation in the *BRAF* gene was detected. The patient started therapy with nivolumab in January 2021 in a standard adjuvant regime. After four cycles of therapy, follow-up thoracic computed tomography (CT) imaging showed mediastinal lymph nodes enlarged up to 28 mm in diameter (Figures 1a and 1b). From the diagnosis of primary melanoma in October 2018 until the observed enlarged mediastinal lymph nodes, the patient

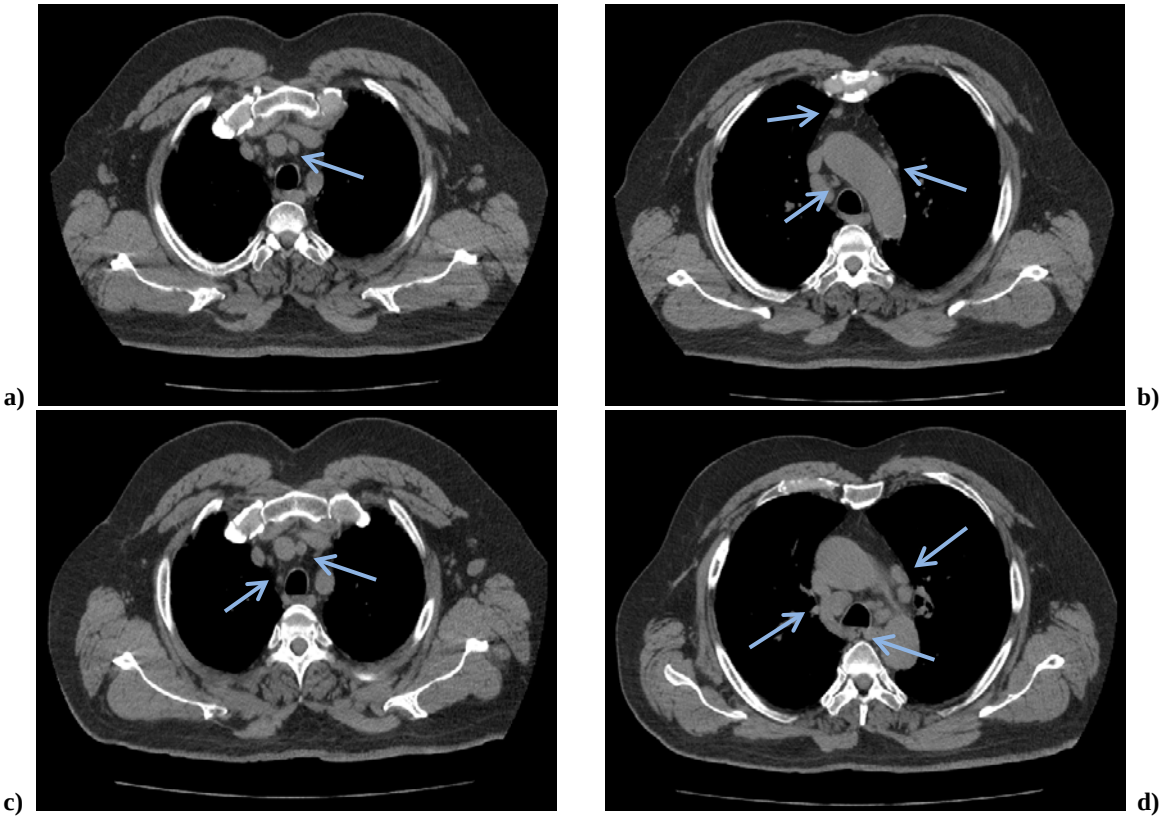
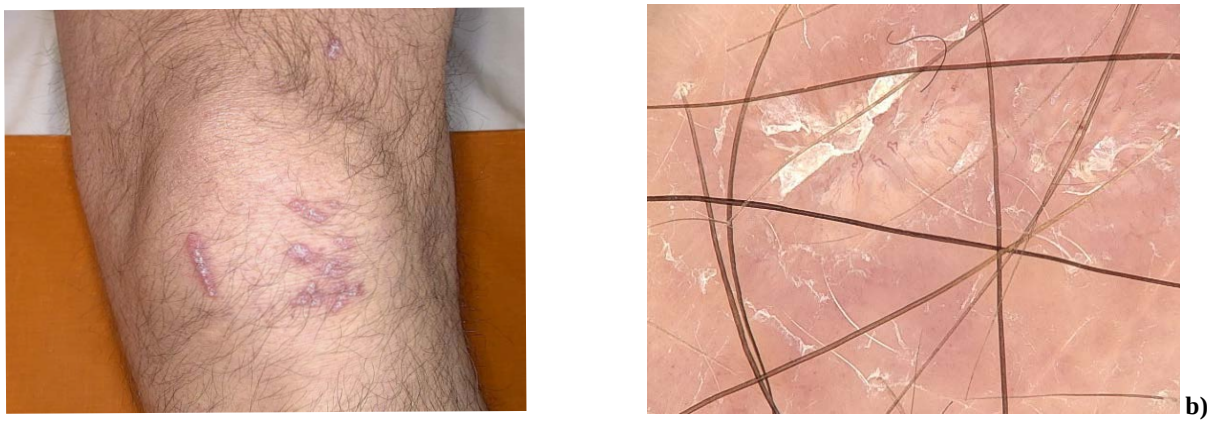


Fig. 1 – Mediastinal lymphadenopathy (blue arrows) after 4 cycles of nivolumab therapy up to 28 mm (a,b) and after 12 cycles of nivolumab therapy up to 17 mm (c, d).

underwent full body CT images every six months, which were completely normal. After 12 cycles of therapy, thoracic CT imaging showed persistence of the enlarged mediastinal lymph nodes (Figures 1c and 1d). Furthermore, grouped brownish-red papules and plaques covered with whitish scales were observed on the skin of the lower legs (Figure 2a) and dermatoscopy revealed a pattern of granulomatous inflammation – the presence of yellowish-orange globular fields, permeated with linear blood vessels (Figure 2b). HP analysis of the skin sample revealed DISR of the skin (Figure 3a). Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy were taken, and HP analysis was consistent with chronic granulomatous inflammation (Figure 3b). Histochemical analyses showed no visible Periodic acid-Schiff (PAS)-sensitive fungal or acid-resistant mycobacterial infectious agents (Ziehl-Nielsen). The 24-hour urine calcium was slightly elevated, the angiotensin-converting enzyme (ACE) level was normal, and the QuantiFERON® TB test was negative. Therapy with oral prednisone 60 mg daily in decreasing doses in the next three months was started, and nivolumab therapy was discontinued after 12 cycles due to the observed progression of the disease in the form of in-transit metastases. After three months, skin lesions on the lower extremities were in regression, leaving hyperpigmented macules, and after 16 months, there was a confirmed complete remission of the enlarged mediastinal lymph nodes.

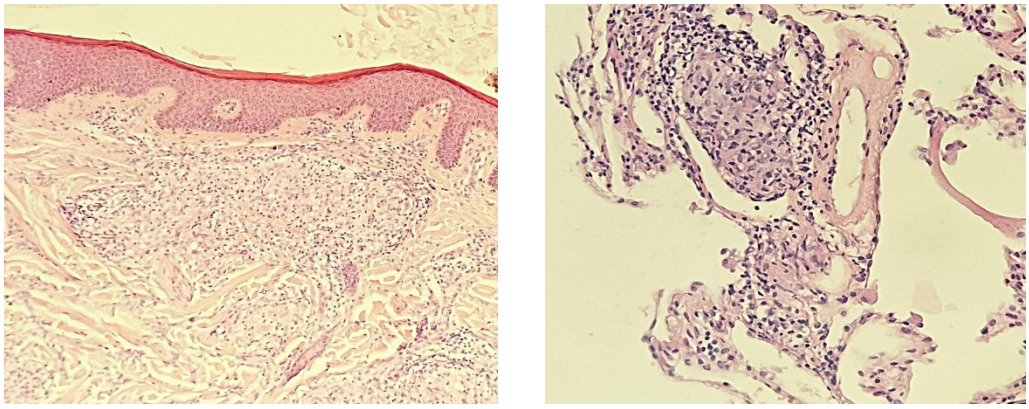
Case 2

A 45-year-old man has been diagnosed with nodular melanoma (Breslow thickness 5.2 mm, Clark level IV with ulceration) in February 2016, followed by re-excision and SLNB of the left inguinal region, without metastasis in the lymph nodes. Excision of in-transit metastases was performed in February, May, and October 2019. BRAF testing was performed, and mutation in the *BRAF* V600 gene was detected. From December 2019 to December 2020, adjuvant therapy with dabrafenib and trametinib was carried out. In July 2021, new in-transit metastases were excised, and in October 2021, adjuvant therapy with pembrolizumab was started. After four cycles of adjuvant therapy with pembrolizumab, follow-up thoracic CT imaging showed enlarged mediastinal lymph nodes (Figures 4a and 4b). From the diagnosis of melanoma, during the application of adjuvant target therapy until the detection of mediastinal lymphadenopathy, CT imaging of the whole body was performed every six months, with



a) **b)**

Fig. 2 – Grouped brownish-red papules and plaques covered with whitish scales in the skin of the knee, after 12 cycles of nivolumab therapy (a); Dermatoscopy of the changes on the knee reveals a pattern of granulomatous inflammation – the presence of yellowish-orange globular fields, permeated with linear blood vessels (b).



a) **b)**

Fig. 3 – Histopathological (HP) analysis of the skin sample (a) reveals the sarcoidosis-like reaction of the skin and HP analysis of the transbronchial biopsy (b) point out to the pattern of chronic granulomatosis inflammation (hematoxylin and eosin, ×10).

completely normal findings. Bronchoscopy with BAL revealed granulomatous inflammation and transbronchial biopsy confirmed sarcoidosis on HP analysis (Figures 5a and 5b). The 24-hour urine calcium was normal, the level of ACE was slightly elevated, and the Quantiferon TB test was negative. Therapy with oral prednisone 40 mg daily in decreasing doses in the next three months was performed, and pembrolizumab therapy was continued until the planned completion after nine cycles. After adjuvant therapy with pembrolizumab was completed, remission of enlarged mediastinal lymph nodes occurred (Figures 6a and 6b).

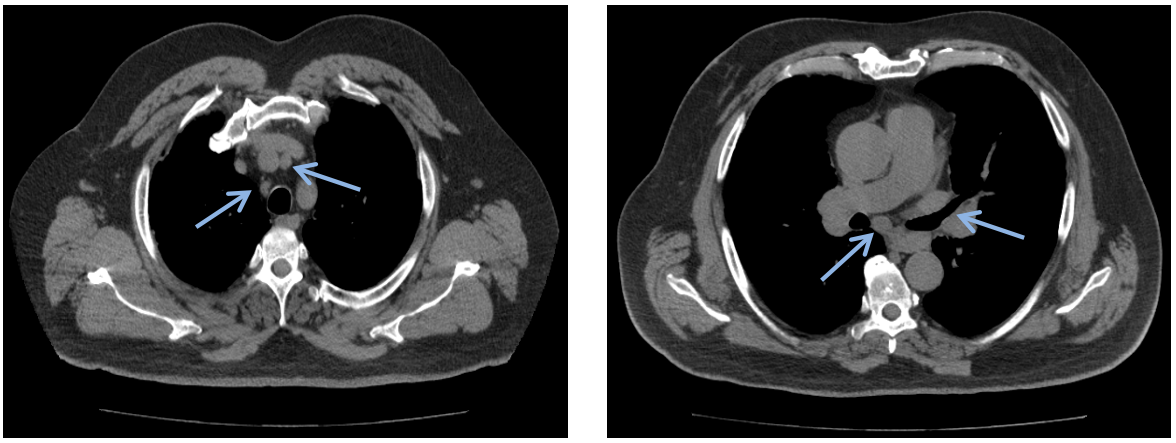
a)  b)

Fig. 4 – Mediastinal lymphadenopathy (blue arrows) after 4 cycles of pembrolizumab therapy up to 22 mm (a, b).

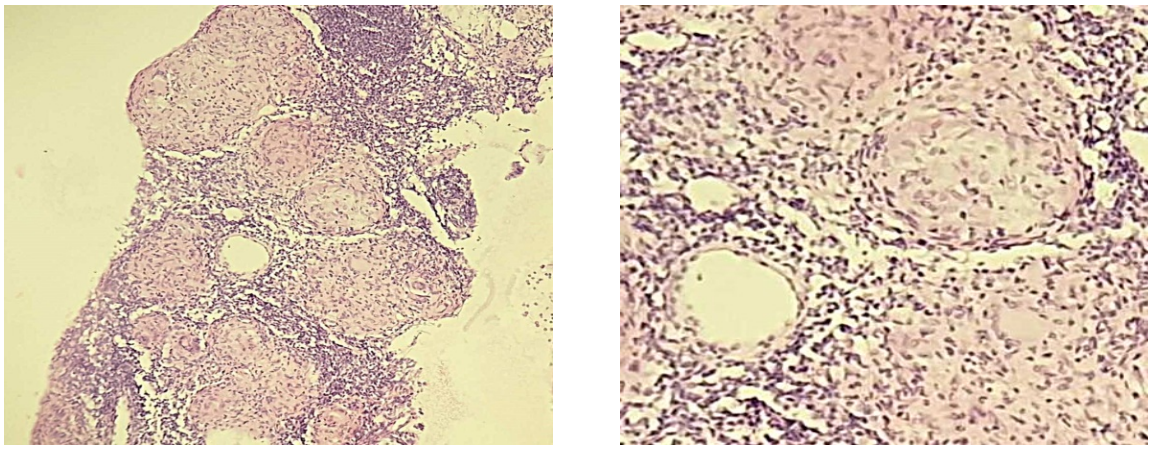
a)  b)

Fig. 5 – Histopathological analysis of the transbronchial biopsy point out to the pattern of chronic granulomatosis inflammation [hematoxylin and eosin, ×10 (a); ×20 (b)].

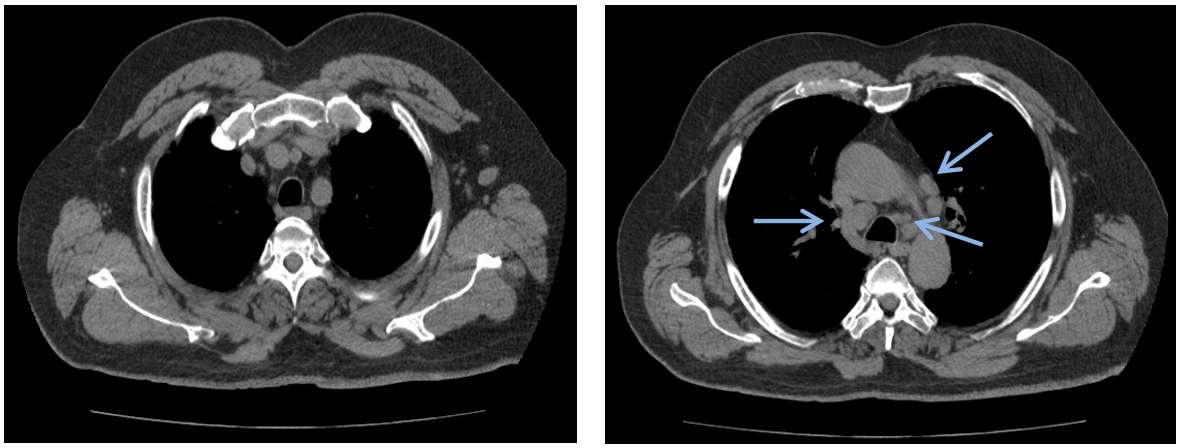
a)  b)

Fig. 6 – Mediastinal lymphadenopathy (blue arrows) after 9 cycles, that is the completion of adjuvant therapy with pembrolizumab up to 10 mm (a, b).

Discussion

Current treatment options for melanoma, such as immunotherapy, have significantly changed the prognosis of patients with advanced melanoma. With the increase in the number of patients receiving immunotherapy, new AEs of the therapy are discovered, and new knowledge is gained in diagnosing and treating already well-described AEs. DISR is a systemic granulomatous tissue reaction that is indistinguishable from sarcoidosis and occurs in a temporal relationship with the initiation of an offending drug, such as ICIs, tumor necrosis factor (TNF)-alpha (α) antagonists, interferons (IFNs), antiretroviral therapy, and others [2]. Histopathologically, DISR granulomas most often completely resemble sarcoid granulomas with the presence of non-caseous epithelioid granulomas of giant cells surrounded by lymphocytes, as well as with the occasional presence of birefringent foreign bodies, asteroid bodies, and Schaumann bodies [3–6]. Anti-programmed death-1 (PD-1) antibodies promote $CD4^+$ T-lymphocyte activation [T helper (Th) type 1 – Th1 and Th17 cells] and cytokine secretion, including IFN-α, TNF-α, IL-17, and IL-2, which may be the cause of DISR [7]. In a retrospective study of patients treated with ICIs at the University of California Medical Center, DISR occurred in approximately 3.7% of patients treated with anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) or anti-PD-1 antibody and 6.3% of patients treated with a combination of both [1]. In the same study, the median interval from initiation of immunotherapy to the development of DISR was 5.5 months. The median interval from radiologic detection of DISR to evidence of resolution was 5.8 months [1]. In contrast, in a review of the literature by Melin et al. [8], the median time to onset of symptoms associated with granulomatosis after the introduction of immunotherapy was three months. Although it is a rare cutaneous immune-mediated AE, sarcoidosis has been shown to occur more frequently in melanoma patients treated with immunotherapy than in those treated for other cancers [9–11]. Previous studies have shown that the most commonly affected organs are lymph nodes, lungs, skin, and eyes [8, 12–14]. Previous research has shown that the diagnosis of DSIR is established by excluding alternative causes of granulomatous inflammation as well as idiopathic sarcoidosis, with certain specific etiologies that require special attention [2]. It is always necessary to rule out an underlying malignancy (disease progression) first because the neoplastic lymph node involvement detected by CT/positron emission tomography studies can mimic sarcoidosis [15]. Therefore, in many cases it is important to confirm HP diagnosis in any new or growing enlargement of lymph nodes, most often hilar and mediastinal, in patients in whom we suspect DSIR. Certainly, in the case of skin changes, it is always necessary to perform a dermatoscopic examination and a biopsy of the lesion to eliminate the suspicion of cutaneous/subcutaneous metastases. As both interstitial lung disease and interstitial pneumonitis represent one of the possible side effects of immuno-oncology therapy, it is sometimes difficult to distinguish them from pulmonary sarcoidosis. What can help us in the differential diagnosis of these two AEs is that pulmonary sarcoidosis caused by immunotherapy is usually asymptomatic or with milder symptoms, while pneumonitis is usually accompanied by respiratory symptoms [16]. Excluding pulmonary infections can also be challenging based on radiological imaging alone, in which case, clinical correlation and laboratory findings are crucial [17]. In most cases of ICI treatment, DISR has been reported to improve after discontinuation of ICI [7]. In a study by Cornejo et al. [18], 57% of patients received systemic corticosteroids, 49% had withholding or discontinuation of immunotherapy, whereas 17.9–41% of individuals used systemic corticosteroids in other trials [16, 19]. Looking at the data from the available literature and comparing it with idiopathic sarcoidosis, DSIR, in most cases, has milder clinical manifestations, better prognosis, and less need for systemic corticosteroids or other immunosuppressive therapy [12, 20, 21]. It has not been established yet why this is so, but it is considered that it is most likely because of an earlier diagnosis of DSIR compared to idiopathic sarcoidosis due to the regular radiological controls and clinical examination of these patients. The Society for Immunotherapy of Cancer Toxicity Management Working Group has issued useful consensus guidelines for the management of ICI-related DSIR. The guidelines are as follows: in grade 1 of pulmonary sarcoidosis, consider the use of corticosteroids, continue immunotherapy, and closely monitor the patient; in grade 2, or when progressive radiographic changes with persistent and/or disturbing pulmonary symptoms occur, along with the worsening of the lung function, simultaneous involvement of critical extrapulmonary organ systems, or hypercalcemia associated with sarcoidosis, it is necessary to start systemic corticosteroid therapy (prednisone 1 mg/kg or IV equivalent of methylprednisolone with taper steroids over 2–4 months, depending on response) [22]. The main goal in these patients is certainly to avoid discontinuation of therapy, especially in patients with a good response, but the occurrence of grade 2 or higher immune-related AEs most often leads to discontinuation of ICIs [23]. The results of previous studies suggest that ICI can be safely continued in DSIR grade 1 [7, 12]. Results obtained from a literature review by Melin et al. [8] suggest that the occurrence of a granulomatous reaction during ICI treatment may be associated with clinical benefit. The observed response rates (75% and 69%, respectively) are higher than those typically reported with ICIs (about 43% for anti-PD-1 and 58% with the combination of ipilimumab plus nivolumab) [8]. We conducted a literature review of ICI-induced sarcoidosis in patients treated for melanoma. In total, we found 88 patients described. The majority of patients are men (52%), and the most common localization is the thoracic region, skin, and lymph nodes. All other relevant data obtained from the literature review are presented in Table 1 [3, 8, 9, 11, 19, 24–67]. Certainly, further research and a larger number of patients are needed to prove this data.

Table 1

Patient characteristics from literature review (n = 88) [24–67]

Parameter	Value
Gender	
female	42 (48)
male	46 (52)
Age (years), mean (range)	56 (22–83)
Type of ICIs	
anti-CTLA-4 monotherapy	23 (26)
anti-PD-1 monotherapy	34 (39)
anti-CTLA-4 + anti-PD-1 combined	31 (35)
Time since ICI initiation (months), median (range)	3 (1–43)
Sites and organs involved with granulomatous reaction	
thoracic	69 (78)
dermatological	36 (41)
lymph node	8 (9)
bone	5 (6)
hepatic	4 (5)
ophthalmologic	2 (2)
renal	1 (1)
Therapeutic management for DSIR	
systemic corticosteroids	34 (39)
discontinuation of immunotherapy	40 (45)
Response to treatment of DSIR (n = 83)	
stability	17 (20)
partial or complete regression	66 (80)

ICIs – immune checkpoint inhibitors; CTLA-4 – cytotoxic T-lymphocyte associated antigen-4; PD-1 – programmed death-1; DSIR – drug-induced sarcoidosis-like reaction.
Values are given as numbers (percentages) except for age and time since ICI initiation.

Conclusion

ICI-induced sarcoidosis has been reported in different cancers and using different ICIs. Further larger multicenter studies are needed to reveal the true incidence of DISR in melanoma patients treated with ICIs. Certainly, all previous research and case reports support the fact that the most common localizations of DISR are the lymph nodes, lungs, and skin. The differential diagnosis of DISR vs. melanoma progression requires a biopsy of the suspicious lesion in the majority of cases, but an interdisciplinary approach is always needed to distinguish the true progression of the disease from an adverse reaction, as well as to decide to continue ICIs. In most cases, it is not necessary to discontinue ICIs. Usually, the changes resolve or regress spontaneously after discontinuation of therapy, which should be considered in the adjuvant setting. Sometimes it is necessary to start standard therapy with systemic corticosteroids, which, in most cases, have shown a good therapeutic response.

Conflict of interest

The authors declare no conflict of interest.

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