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The diagnosis and management of sarcoid-like reactions in patients with melanoma treated with BRAF and MEK inhibitors. A case series and review of the literature

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***Abstract*:** Sarcoidosis and sarcoid-like reactions (SLR) have been repeatedly reported in patients with melanoma treated with BRAF and MEK inhibitors. In the current study we present three patients that developed SLR under treatment with BRAF and mitogen-activated protein kinase (MEK) inhibitors for melanoma. Two patients developed mediastinal lymphadenitis with histological features of an SLR while on targeted therapy in the adjuvant setting, whereas one patient with metastatic melanoma developed granulomatous nephritis while receiving combination treatment with BRAF/MEK inhibitors and atezolizumab. In addition, we review the published literature on the pathogenesis, clinical characteristics, histologic features, imaging findings, and other potential useful diagnostic tools. We also address the need for a common terminology for these cases and propose an algorithm for the accurate diagnosis of BRAF/MEK inhibitor-induced SLR. We also review the currently available data on the treatment of these patients and suggest a treatment approach for SLR in patients with melanoma, as well as for the management of melanoma when SLR emerges.

Keywords: sarcoidosis, sarcoid-like reaction, BRAF inhibitor, melanoma, targeted therapy

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Introduction

Sarcoidosis is a multisystem, granulomatous disease of unknown origin that, among others, has been correlated with cancer, especially lymphomas, renal and gastrointestinal cancers, and sarcomas. In addition, sarcoid-like reaction (SLR) is a histologic feature found occasionally in metastatic lymph nodes.[1] In one study of 1199 patients with melanoma, sarcoidosis was reported in 0.58% of cases, in the era before the development of new antimelanoma treatments.[2] Despite this, sarcoidosis and granulomatous inflammation is increasingly being reported during the last few years of in patients with melanoma under treatment with BRAF and mitogen-activated protein kinase (MEK) inhibitors. Several granulomatous inflammatory lesions have been reported, including skin and ocular lesions, lymph nodes and pulmonary lesions, and, less commonly, involvement of the kidney, heart, or nervous system. Apart from BRAF and MEK inhibitors, granulomatous reactions have been reported with other targeted therapies, such as tumor necrosis factor alpha (TNFα) inhibitors, immune checkpoint inhibitors, and other cytokine modulators.[3]

In the present article, we present three cases of patients with melanoma that developed granulomatous inflammation under treatment with BRAF and MEK inhibitors. We describe the clinical characteristics of the patients, the histologic features of the lesions, the diagnostic procedure, and the management of the patients. In addition, we provide a comprehensive review of the literature on BRAF and MEK inhibitor-induced sarcoid-like reactions (BRAF/MEKi-induced SLR) in patients with melanoma, as well as an algorithm for the diagnosis and differential diagnosis

of BRAF/MEKi-induced SLR from melanoma progression. We also attempt to formulate guidelines for the management of sarcoidosis in patients with melanoma, as well as for the management of melanoma when granulomatous inflammation emerges. All three patients provided written informed consent for the publication of their data.

Case presentation

Case 1

A 45-year-old Caucasian female with insignificant past medical history was diagnosed with a cutaneous malignant melanoma of the right femoral region. The primary lesion was resected and histology demonstrated a superficial spreading melanoma of Breslow thickness 3.2 mm, with ulceration. She then underwent a wide resection of the primary lesion as well as right inguinal sentinel lymph node excision. Wide resection margins were negative, whereas the sentinel lymph node was infiltrated. As a result, the patient underwent right inguinal lymph node dissection, which identified lymph node metastases in 2 out of 7 lymph nodes. Clinical examination and computed tomography (CT) of the brain, chest, abdomen, and pelvis did not reveal findings suggestive of distant metastatic disease. The pathology stage by American Joint Committee on Cancer (AJCC) (7th edition) was pT3b, N2a, M0 (stage IIIB). In addition, molecular tumor analysis showed a BRAFV600E mutation.

The patient was started on adjuvant treatment with dabrafenib at a dose of 150 mg, twice daily and trametinib at a dose of 2 mg, once daily. During the first three months of treatment, she experienced recurrent episodes of low-grade fever, accompanied by nodular panniculitis of both lower limbs, which resolved after temporary treatment interruption. Following this, the drugs were well tolerated, with no evidence of disease recurrence; the patient discontinued treatment after a total treatment duration of 12 months. At CT restaging upon discontinuation, multiple, enlarged mediastinal lymph nodes were identified without pulmonary parenchymal lesions. In contrast, in previous restaging CT scans performed every three months while on treatment, no such lesions were present. The patient underwent bronchoscopy and transbronchial biopsy of a mediastinal lymph node. Histology revealed the presence of noncaseating epithelioid granulomas, suggestive of a sarcoid-like reaction (Figure 1). Complete blood count and biochemistry were normal. Serum angiotensin-converting enzyme was also normal. A QuantiFERON-TB Gold assay was negative. The patient remained asymptomatic, did not receive treatment, and during a 3-month follow-up, a CT scan showed regression of mediastinal lymphadenopathy and no evidence of melanoma metastases.

Case 2

A 38-year-old Caucasian male was diagnosed with a stage IIIc (TX, N3, M1a) malignant melanoma. The patient had no known risk factors for melanoma. He was treated with interferon α in an adjuvant setting; however, three years later he experienced an episode of gastrointestinal bleeding. After an enterectomy, this proved to be due to metastatic melanoma in the jejunum. The lesions were found positive for the V600E mutation of the *BRAF* gene. A CT scan performed a month later revealed two enlarged mesenteric lymph nodes; the patient was started on vemurafenib at 960 mg, twice daily and cobimetinib at 60 mg, once daily, for 21 days, followed by 7 days off, in the context of a phase III, randomized, blinded clinical trial (ClinicialTrials.gov identifier: CO39262/IMspire 150).[4] As per protocol, atezolizumab at 840 mg every two weeks was added to the regimen after the first 4 weeks of treatment with vemurafenib and cobimetinib. Four months after treatment initiation, the patient achieved a complete remission (CR).

Fifteen months since treatment initiation, the patient experienced a gradual decline of his renal function, evidenced by a decrease of his estimated glomerular filtration rate (eGFR), along with subtle proteinuria (0.34 g/24h) with no arterial pressure changes. His serum creatinine level was 1.81 mg/dl (baseline value being 0.75 mg/dl) corresponding to an eGFR of 44 ml/min/1.73 m^2. The patient's hemoglobin level also decreased to 10.2 g/dl from a baseline of 12.4 g/dl. No metabolic acidosis was found. His erythrocyte sedimentation rate was 65 mm/h, with no c-reactive protein increase. There was no increase in urine leukocytes and a urine culture was found negative. A kidney and renal arteries ultrasound revealed no findings, while a positron emission tomography (PET)-CT scan confirmed a sustained CR of his advanced melanoma. Treatment with vemurafenib and cobimetinib was temporarily withheld and his renal function improved; however, upon re-initiation of treatment, his

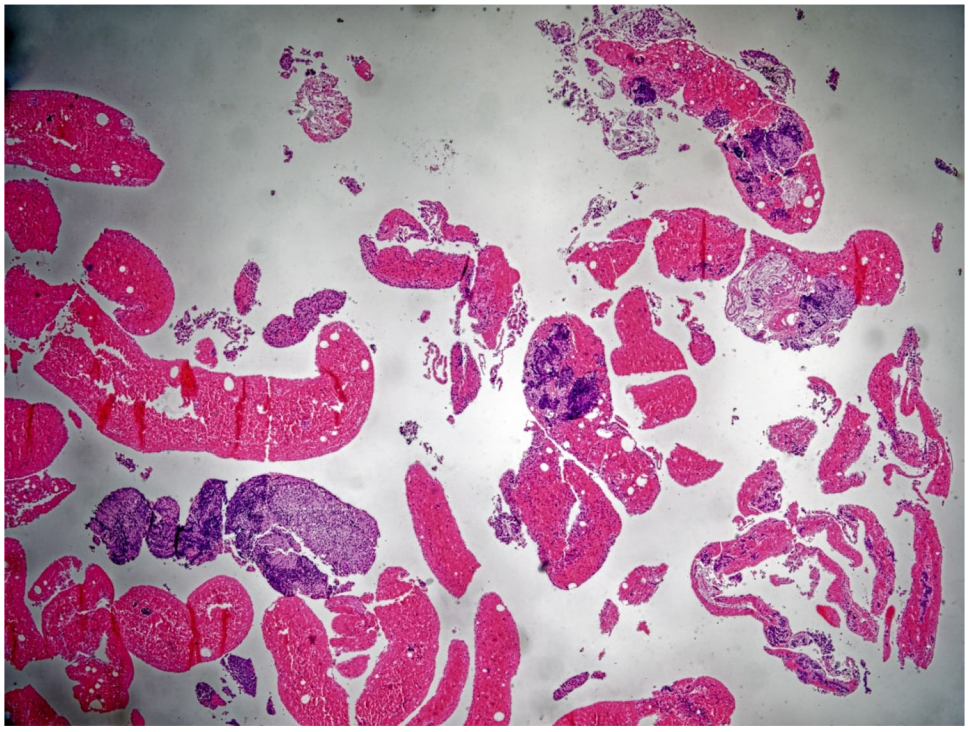

Figure 1. Hematoxylin and eosin stain (10×) demonstrates few non-necrotizing sarcoid-like epithelioid granulomas. Multinucleated giant cells are not present.

eGFR declined once again (serum creatinine of 2.70 g/dl, eGFR 31 ml/min/1.73 m^2) and the drugs were once more discontinued. Atezolizumab was also temporarily discontinued and a renal biopsy was performed. The histologic evaluation revealed the presence of non-necrotizing granulomas in the interstitial space (Figure 2), findings indicative of a granulomatous nephritis. In addition, a tuberculin skin test was negative, as was a urine culture for *Mycobacterium tuberculosis*. Vemurafenib and cobimetinib were permanently discontinued and the patient was started on methylprednisolone at 0.75 mg/kg/day for a week, with rapid tapering during the following month. After the first week of corticosteroids, the patient's eGFR normalized, while treatment with atezolizumab was resumed. Twenty-nine months after resuming treatment, the patient is still in CR under atezolizumab, without any renal function impairment.

Case 3

A 54-year-old Caucasian woman was diagnosed at the age of 48 with a BRAF-mutated, stage IIIc (T3b, N1a, M0) melanoma on her left calf. She was treated with interferon α in the adjuvant setting, but two years letter an in-transit lesion on her left thigh emerged and was excised. She was then treated with ipilimumab, but treatment was discontinued due to hypophysitis. A year later, she developed a subcutaneous nodule on her chest, the histologic examination of which was consistent with a metastasis. She was treated with nivolumab, at 240 mg every two weeks, but six months later she experienced a grade-3 increase of the liver enzymes [serum glutamic oxaloacetic transaminase (SGOT)/serum glutamic pyruvic transaminase (SGPT)] and nivolumab was permanently discontinued. She was then started with dabrafenib at 150 mg twice a day and trametinib at 2 mg once a day in the adjuvant setting. The patient experienced recurrent panniculitis lesions on both lower limbs and the abdominal wall during the first four months of treatment; nine months after treatment initiation, upon her 3rd imaging assessment of response, several enlarged paratracheal, subcarinal, aortopulmonary window, and hilar lymph nodes were found without any parenchymal lung lesions. No other signs of disease progression were found. The patient underwent a bronchoscopy and an endobronchial ultrasound-guided biopsy (EBUS–TBNA) of one of the subcarinal lymph nodes. The histologic

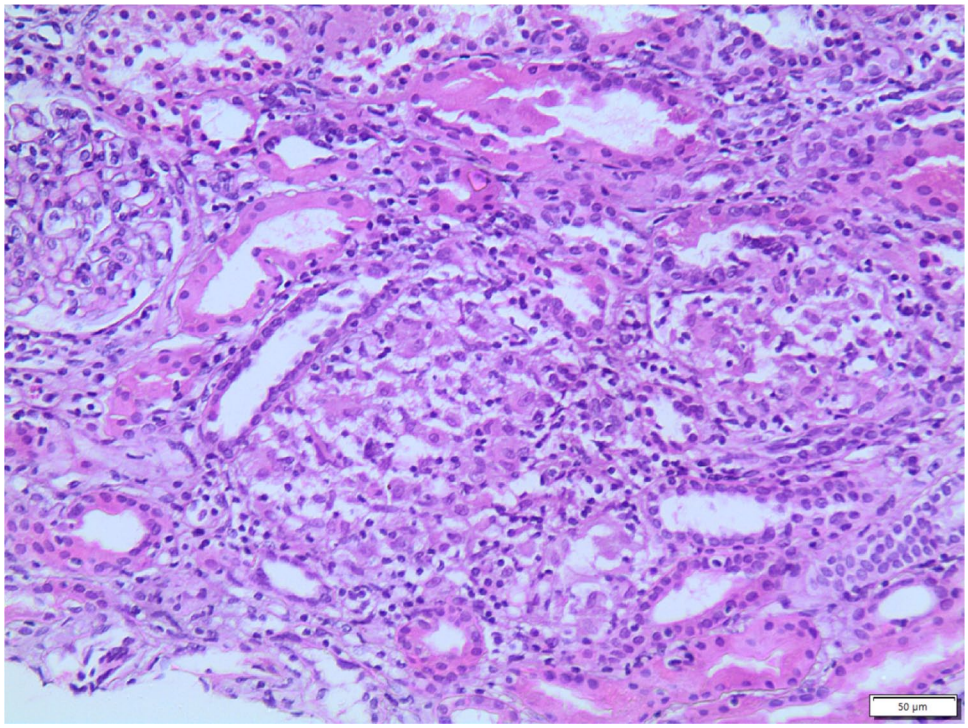

Figure 2. Confluent, non-necrotizing, well-formed granulomas in the renal interstitium, composed of epithelioid histiocytes, monocytes, lymphocytes, and a few multinucleated cells.

evaluation of the lesions revealed epithelioid non-caseating granulomas without multinucleated giant cells, suggestive of a SLR. Her complete blood count, biochemistry profile, and serum angiotensin-converting enzyme (sACE) levels were within normal limits while an interferon gamma release assay (IGRA) was found to be negative. The patient received no treatment for these lesions and continued treatment with dabrafenib and trametinib without any dose reduction. Eight months later, she is still in complete remission, with no change in the number and/or size of the lymph nodes. Scarce erythema nodosum lesions still come up on her legs but are well-tolerated.

Discussion

Classification: Sarcoidosis, targeted therapy-induced SLR, or melanoma-induced SLR?

Granulomatous inflammation has been repeatedly reported in patients treated with BRAFi's and MEKi's. However, there is great heterogeneity in the terminology used for the reported cases. Lheure *et al.*[5] reported 4 cases of sarcoidosis in patients treated with vemurafenib, whereas patients with only one clinical feature of sarcoidosis were considered to display an SLR. Adam *et al.*[6] also reported two cases of sarcoidosis. In contrast, Huynh *et al.*[7] used the term SLR for all reported cases of granulomatosis, in the absence of data regarding the potential influence of infectious agents and genetic predisposition. Several cases have been reported as granulomatous involvement of specific organs, e.g., granulomatous myocarditis,[8] hepatitis,[9] nephritis,[10] uveitis,[11] and dermatitis.[12–16] Cases of systemic sarcoid-like granulomatosis have also been reported.[17] Finally, Dando *et al.*[3] reviewed all the above reported cases using the term 'drug-induced SLR'.

Sarcoidosis is a systematic disease characterized by non-necrotizing granuloma formation. However, the presence of granuloma alone is not equivalent to sarcoidosis, since diagnosis also relies on the compatible clinical presentation and, most importantly, the exclusion of other causes of granulomatous inflammation. These include, among others, drug-induced granulomatosis and SLRs in cancers and lymphomas.[18,19] Recent data suggest that sarcoidosis patients are genetically predisposed, yet genetic predisposition criteria have not been established nor implemented in clinical routine so far.[20,21] As a result, sarcoidosis

actually represents an 'autonomous' disease. as opposed to drug-induced sarcoidosis/SLR. Despite this, the exact pathogenesis of both conditions has not been elucidated: it is unknown whether the drug acts as a trigger in patients with genetic predisposition, whether it exacerbates subclinical sarcoidosis, or whether it causes granulomatous reaction, distinct from sarcoidosis.[22] In addition, 'true' sarcoidosis could incidentally occur concurrently with the initiation of a drug. There are no histologic criteria to support a distinction between sarcoidosis and drug-induced SLR granuloma. The temporal association with drug initiation, as well as the potential resolution or improvement with drug discontinuation and recurrence with drug re-challenge are features that may help to distinguish between drug-induced SLR and 'true' sarcoidosis.[22,23]

In addition, both sarcoidosis and drug-induced sarcoidosis/SLR should be distinguished from malignancy-induced SLR. However, melanoma-induced SLR cases are rare. The reported prevalence of sarcoidosis in 1199 melanoma patients before the introduction of targeted therapy was 0.42% (after exclusion of 2 cases related to immunotherapy).[2] In a recent review, Beutler and Cohen[24] identified only 17 cases of melanoma-associated sarcoidosis. Malignancy-induced SLR usually occurs in the vicinity of the primary tumor, in the draining lymph nodes, or near a metastasis; whereas, involvement of non-regional tissues is less frequent.[23] Immunohistological studies suggest that malignancy-induced SLR granulomas contain B-cell lymphocytes and sinus histiocytes that are not observed in sarcoid granuloma.[25,26]

With regard to melanoma patients treated with BRAF/MEKi's, Dando *et al.*[3] reported that the average onset of SLR after drug initiation was 9 months (range 1–21) and only one patient had a history of sarcoidosis that relapsed after vemurafenib introduction.[4,16] Targeted Treatment (TT) discontinuation should be avoided in melanoma patients unless absolutely indicated. Only 10 patients (including 2 patients reported here) discontinued. In all other patients described above the lesions resolved soon after drug discontinuation. Taking the above clinical features into consideration, and in the absence of immunohistological data, we believe that 'BRAF/MEKi -induced SLR' is the most appropriate term.

Pathogenesis

Patients under treatment with BRAFi's have been shown to have increased serum levels of tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ),[27] which may promote granuloma formation.[4] In addition, Lheure *et al.*[5] observed a decrease in absolute lymphocyte counts in 3 out of 5 patients during vemurafenib treatment and proposed that this decrease may be due to the recruitment of CD4+ T lymphocytes to the organs affected by the melanoma. They proposed that this CD4+ T-cell recruitment may constitute an immune response to the various melanoma antigens stimulated by vemurafenib.[4] Park *et al.*[12] reported a patient who developed a granulomatous reaction on dabrafenib and trametinib that was biopsied to show melanoma antigen recognized by T cells (MART-1) and microphthalmia-associated transcription factor (MITF) positive melanoma cells at the center of the granulomatous inflammation. They have also proposed that granulomatous lesions may represent an immune response against targets on melanoma cells, perhaps unveiled by treatment.[11] However, melanoma cells were not identified in granuloma biopsy samples in other studies. In addition, treatment with either a BRAFi alone, or a BRAF/MEKi, has been associated with several immunomodulatory effects on the tumor microenvironment (TME), i.e. an increased expression of melanoma antigens and an increase in CD8+ T cell infiltrate, as well as a decrease in immunosuppressive cytokines [interleukin-6 (IL-6), IL-8] and an increase in markers of T cell cytotoxicity.[28] It is unknown whether these TME changes are durable; many studies have focused on the evaluation of combination therapy (with BRAF/MEKi and immunotherapy) or sequential therapy because the window in which to take advantage of BRAF/MEKi-induced TME changes appears relatively narrow.[29] The long median time to SLR after treatment with targeted therapy could denote a long-term immunomodulatory effect of these agents.

Despite this, there is paucity of data regarding the potential immunomodulatory effect of BRAFi's and MEKi's on the TME in the adjuvant setting. Interestingly, in the current study, two patients developed drug-induced SLR while on adjuvant treatment with BRAFi's and MEKi's (cases 1 and 3) whereas all previously reported cases involved patients with unresectable and metastatic disease.

Further studies are needed in order to assess the immunomodulatory effect of BRAF/MEKi's when used in the adjuvant setting.

Clinical presentation

The reported incidence of histologically-confirmed sarcoidosis or SLR among monocentric retrospective studies is 5.7%, and 11% in patients treated with vemurafenib monotherapy and dabrafenib/trametinib combination, respectively.[4,6] The onset ranges between 1 and 21 months after treatment initiation, with an average range of 9 months.[17]

The skin represents the most common site of involvement, with a reported incidence of 83% in a review of 30 cases.[17] Interestingly, skin involvement occurs in only 16–32% of patients with sarcoidosis.[19] In addition, it is the site of SLR onset in the majority of cases.[30] Skin SLR presents more commonly with papules and plaques, but can also appear as subcutaneous nodules on the arms or legs, both early and late after treatment initiation.[4,6,9,11–14,31,32] Finally, Korman *et al.*[33] reported a case of granulomatous dermatitis within a benign blue nevus. Granulomatous infiltration of tattoos has also been reported.[34] Reviewing 37 identified cases of SLR (including the three cases presented here), 86.3% of patients treated with combination therapy and 71.4% of patients treated with a BRAFi monotherapy had skin involvement. In addition, the skin was the only affected organ in 63.6% and 27.3% of the patients, respectively.

Similar to sarcoidosis, BRAF/MEKi-induced SLR can also occur in the thorax. The reported patients had no respiratory symptoms and the SLR was discovered unexpectedly during follow-up imaging for the underlying melanoma.[4,5,16] It is important to note that about 50% of reported patients were not investigated for pulmonary-mediastinal disease.

Other systemic manifestations are less frequent, since inflammation of the eyes, liver, kidney, joints, heart, and salivary glands occur in few patients, with symptoms and signs varying depending on the affected organ. Specific sarcoidosis syndromes (Löfgren and Heerfordt) are rare. Lheure *et al.*[5] reported a case of Löfgren syndrome after vemurafenib, as well as a patient with Heerfordt syndrome who relapsed after treatment with vemurafenib. As before, among 37 identified cases with SLR, the involvement of organs other than the skin was reported in 36.4% of patients treated with combination therapy, and 61.5% of patients treated with BRAFi monotherapy. Interestingly, uveitis was reported in 30.7% of patients treated with monotherapy *versus* 0% of patients treated with combination therapy. Although granulomatous inflammation was histologically confirmed in only one case,[10] it is unknown whether the remaining cases represent an SLR or a vemurafenib-induced uveitis.

Finally, in sarcoidosis, many symptoms are not caused by granulomas in a specific location, but result from the release of mediators, such as fatigue and post-sarcoidosis fatigue syndrome,[19] which have not been reported in melanoma patients with BRAF/MEKi-induced SLR.

Diagnosis

Histology. When SLR is suspected, a biopsy of the affected organ and histologic examination should be performed. Histopathology findings from reported cases are identical to those of sarcoidosis. In the case of subcutaneous nodules, which may be a feature of BRAFi -induced panniculitis or may represent an SLR, histology can also be helpful. In a case series of BRAF-inhibitor-induced panniculitis, histology revealed neutrophilic infiltration in cases presenting in earlier stages of treatment and lymphocytic predominance in those lesions presenting later in the course of treatment, with lobular involvement (more commonly than with septal component) and/or evidence of vasculitis.[35] In contrast, in cases of BRAF/MEKi-induced skin SLR, histology of papules revealed sarcoidal granulomas, while histology of subcutaneous nodules identified septal panniculitis consistent with erythema nodosum in some cases,[3] as well as a lobular pattern of panniculitis with a predominantly lymph histiocytic infiltrate forming non-necrotizing granulomas, a scarcity of neutrophils, and no evidence of vasculitis.[12]

According to guidelines for the diagnosis of sarcoidosis, histology can be deferred in cases of sarcoidosis syndromes (Löfgren and Heerfordt) and lupus pernio. Lheure *et al.*[5] reported a case of Löfgren syndrome under treatment with vemurafenib, as well as a case with a previous history of Heerfordt syndrome, presenting with bilateral non-granulomatous uveitis 7 months after vemurafenib initiation.[4] Histology was not performed

in either case. We believe that if no alternative explanation exists, biopsy could be avoided in such patients.

Other diagnostic tools. Although histology is the cornerstone of SLR diagnosis, further evaluation may be needed in order to assess the extent of disease and number of organs involved. In addition, it is necessary to support the diagnosis in cases where histology is not feasible, and, most importantly, to exclude other causes of granulomatosis, such as infections (e.g. mycobacterial and fungal infections, cat-scratch disease etc.).

Laboratory findings. Hypercalcemia, lymphopenia, elevated sACE, and hypergammaglobulinemia, all associated with an increased likelihood of sarcoidosis[36–38] are rarely reported in patients with BRAF/MEKi-induced SLR and can be normal or mildly elevated.[4,5,10,16] However, the measurement of sACE levels can be useful in cases of ocular involvement where biopsy is not always feasible.[39] In a case provided by Eser Öztürk and Süllü,[11] increased sACE levels, along with findings from ocular examination supported the diagnosis.[10]

Several other laboratory abnormalities may be identified, depending on the organ involved. Patients may present with elevated serum creatinine, with subtle or no proteinuria (consistent with the histologic diagnosis of interstitial nephritis) in cases of kidney involvement,[9] and with abnormal liver function tests if hepatitis is present.[8] Most importantly, mildly elevated serum creatine phosphokinase (CPK) was the only abnormality noticed in an asymptomatic patient. This patient subsequently died and autopsy revealed a granulomatous myocarditis.[7] Finally, bronchoalveolar lavage (BAL) examination showed lymphocytic alveolitis in some cases; it is of importance in excluding infectious causes and malignancy.[16]

Imaging. In cases of lung/mediastinal BRAF/MEKi-induced SLR, chest CT demonstrated pneumonitis with ground-glass opacities, nodules, and/or mediastinal lymphadenopathy.[4–6,16] However, these findings can also indicate metastatic disease. Koo *et al.*[40] compared radiologic findings of mediastinal lymph nodes in sarcoidosis, SLR, and malignant lymph nodes using CT and fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT). In contrast with malignant lymph nodes, lymph nodes from SLR tended to be bilateral and larger in size; significantly more lymph nodes measured >1 cm, whereas the total volume of lymph nodes was less than that of the malignant lymph nodes. The diverse metabolic uptake on FDG-PET-CT was not adequate to differentiate metastatic lymphadenopathy from sarcoid-like reaction and sarcoidosis, highlighting the need for tissue diagnosis. Lu and Macapinlac[41] also reported that the FDG distribution pattern, i.e. bilateral hilar and mediastinal lymph nodes in a 'lambda', 'Christmas Tree', or 'butterfly' distribution pattern is more important than maximum standard unit value (SUVmax) in the interpretation of PET/CT.

Little information is available regarding imaging findings in cases of BRAF/MEKi-induced SLR involving visceral organs other than the lung/mediastinum. An abdominal CT of the patient who developed hepatitis revealed splenomegaly without liver abnormalities.[8] In the current study, patient 2 underwent an FDG-PET-CT when kidney dysfunction occurred, which was normal.

Ophthalmologic examination. Ophthalmologic examination with fundoscopy, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICG) may reveal granulomatous uveitis as well as macular oedema and capillaropathy.[10,16] However, as in ocular sarcoidosis,[42] not all patients with uveitis have granulomatous appearance.[4]

Which patients should be suspected of BRAF/MEKi-induced SLR?

Patients treated with TT may present with adverse events (AEs) that are clinically indistinguishable from SLR. It should be noted that BRAFi-induced panniculitis has been reported in 14% of patients and may, as is the case with skin SLR, occur early or late during the course of treatment, with a mean time to onset of 78 days (9–240).[43] It is characterized by tender, erythematous nodular lesions on the upper and lower limbs and trunk. Uveitis is also a common side effect of treatment with BRAFi's. Kidney impairment, myocardial dysfunction, uveitis, musculoskeletal events, hepatitis, and, rarely, pneumonitis, have also been reported in patients treated with BRAF/MEKi combinations.[44] It should be noted, however, that the majority of patients with SLR present with multi-organ involvement, with the skin being the most common site. Skin manifestations present concurrently or may precede the

extracutaneous manifestations. Interestingly, two of the patients reported in the current study had developed panniculitis prior to the onset of mediastinal lymphadenopathy. Lesions were not biopsied, given that the lesions resolved spontaneously and considering the fact that panniculitis is a well-known adverse event of therapy with BRAFi's. In addition, the number of affected organs may change over time. In contrast, single-organ involvement, other than in the case of the skin. is rare. Therefore, SLR should be considered in the differential diagnosis of melanoma patients treated with TT who present with compatible skin lesions and in patients with systemic manifestations that occur concurrently or follow skin manifestations.

As previously mentioned, lung/mediastinal SLR can be noticed on surveillance imaging and can be mistaken for melanoma progression. As a result, SLRs should be suspected when the lesions occur concurrently or follow compatible skin manifestations, as well as in the case of patients without evidence of melanoma progression in other organs/sites. In addition, SLR should be suspected if imaging distributing patterns are compatible with sarcoidosis.

Sequential, or even concomitant use of TT and immunotherapeutic agents, the latter in the context of clinical trials, is increasingly applied. As a result, in our study, as well as in previous studies[12,32] two patients had also received immunotherapy prior to (case 2) or concurrently with (case 3) TT. Immunotherapeutic agents have also been associated with the development of SLR.[31,45–48] The exact incidence of SLR in patients treated with immune-checkpoint inhibitors (ICIs) is unknown, but in a cohort of 45 patients treated with nivolumab alone or in combination with ipilimumab, 10 patients developed an SLR,[49] while the incidence of radiologically detected, clinically silent, benign thoracic lymphadenopathy among patients treated with anti-CTLA-4 treatment varied between 5.0% and 6.7%.[50] Case 3 developed an SLR nine months after immunotherapy discontinuation (and subsequent TT initiation); in contrast, in case 2 the SLR did not recur after atezolizumab was resumed. As a result, although the involvement of immunotherapeutic agents in the development of SLRs in our patients cannot be totally excluded, we consider TT to be the causative agents. Little information is available about the clinical and radiographic differences of SLR with regards to the offending type of treatment. Ruvio-Rivas *et al.*[30] reported that peripheral lymph nodes as onset mode were seen more frequently in patients under CTLA-4 inhibitors; in contrast, in patients under BRAF/MEKi's they used to be in the form of specific skin lesions and chest X-ray. In addition, stage I-II was more common in the CTLA-4 and programmed cell death 1 (PD-1) groups than in the BRAF/MEK group examined for pulmonary involvement.[29] However, the data is limited and differential diagnosis is not feasible on a clinical basis.

Management of patients with melanoma and BRAF/MEKi-induced SLR

Following a definitive diagnosis of BRAF/MEKi-induced SLR in patients with melanoma, management should adhere to the general principles of the treatment of sarcoidosis. It is common knowledge that the treatment of sarcoidosis is reserved for symptomatic patients or when vital organs are in danger of permanent damage. Even in non-BRAF/MEKi-related sarcoidosis, data from clinical trials are limited, so most treatment decisions are based on observation and expert opinion and depend on the affected organ. Systemic corticosteroids are the mainstay of treatment for sarcoidosis, while local steroid administration is usually offered for skin lesions. However, there are several unanswered questions regarding the management of BRAF/MEKi-induced SLR. What are the indications for treatment initiation? Should corticosteroids be administered with the same indications and at the same dosing schedules as in non-BRAF/MEKi-related sarcoidosis? Should the regimen of BRAF/MEKi's be changed (dose reduction, temporary, or permanent discontinuation)? Should these drugs be replaced by other treatment options such as immune checkpoint inhibitors or chemotherapy? How should the patients be followed after developing BRAF/MEKi-induced SLR? What is the most appropriate management of resistant/recurrent SLR? Are there any differences when SLR develops in patients treated in the adjuvant setting? And, finally, what is the long-term prognosis of patients with SLR and melanoma?

Indications for treatment – use of corticosteroids. The administration of systemic corticosteroids in patients with melanoma has been traditionally regarded as a risk factor for disease progression. Especially since the introduction of ICIs in the treatment of melanoma, corticosteroids have been

increasingly used for the management of immune-related AEs. As a result, the effect of corticosteroid administration on the disease prognosis may have increased. Indeed, in a recent meta-analysis[51] on the associations of steroid use with prognostic parameters in patients with melanoma, it was shown that patients receiving steroids for any reason had a significantly lower overall survival (OS) and progression-free survival (PFS), but this result was not evident in patients treated with steroids for immune-related AE's (irAEs). It is evident, however, in other studies, that the use of steroids, especially if early in the course of immunotherapy, affects the response to ICIs and OS.[52,53] Since there is no definitive answer as to whether systemic corticosteroids alter the prognosis of melanoma, they should be avoided unless deemed absolutely necessary by the treating physician. In a recent review article on the emergence of sarcoidosis in patients with melanoma treated with ICIs or BRAF/MEKi, among 21 patients with sarcoidosis/SLR under treatment with BRAF/MEKi, 10 had pulmonary sarcoidosis, 18 had specific granulomatous skin lesions, two had arthralgia/arthritis, two had uveitis, one had erythema nodosum, one had renal involvement, and one had central nervous system (CNS) involvement.[30] Treatment was offered in 15 (75%) cases; treatments were reported collectively for all patients and consisted of topical corticosteroids in 9 (45%), systemic corticosteroids in 5 (25%), and hydroxychloroquine or doxycycline in 1 (5%). As a result, the use of systemic corticosteroids for the management of SLR should be discouraged, unless the benefits outweigh the risks from their use. Topical steroids should be preferred for patients with skin lesions, while patients with erythema nodosum are effectively-treated with non-steroidal anti-inflammatory agents, especially if they are accompanied by pyrexia. In addition, lymph node enlargement should not be treated with corticosteroids, while pulmonary sarcoidosis should be treated in symptomatic patients or asymptomatic patients with abnormal lung function.[54] The use of systemic corticosteroids may also be necessary for patients with SLR affecting the kidneys, the CNS, or the heart. Since these cases, however, are extremely rare, the patients should be managed as having non-BRAF/MEKi-induced sarcoidosis. The duration of corticosteroid use should be individualized depending on the severity of symptoms and the withdrawal of BRAF/MEKi's. Our experience shows that corticosteroids given for a few weeks, along with the discontinuation of BRAF/MEKi's, is an effective and long-lasting measure for granulomatous nephritis remission.

Decisions for treatment discontinuation. Most reported cases of granulomatous inflammation or sarcoidosis in patients treated with BRAF/MEKi's, especially those affecting the skin, the lung, or the lymph nodes, are mild and easily managed with corticosteroids. Withdrawal of targeted therapy is an effective way to manage SLR; although the decision for temporary treatment withdrawal is easy in such cases, permanent treatment discontinuation should be avoided, except in cases of vital organ involvement. From the reported cases it is evident that treatment maintenance is feasible in most instances. In a review of 30 patients developing SLR in response to BRAF/MEKi's, the targeted therapy was discontinued in only 8 of them. SLR was managed with topical corticosteroids in 19 and systemic corticosteroids in 6 patients.[3] In this review the authors do not clarify whether patients treated with systemic corticosteroids had to discontinue treatment with BRAF/MEKi's. Despite this, cases with vital organ involvement requiring systemic steroids are uncommon; therefore, safe conclusions about the need for concurrent treatment discontinuation and steroid initiation cannot be made. In the above referenced review, SLR completely resolved in 20 patients (including 7 who had stopped targeted therapy), partially responded in 4, stabilized in 2, and progressed in 3 patients, including one patient that died due to myocardial involvement. Despite this, in case of vital organ involvement, such as in the kidney, BRAF/MEKi discontinuation is the preferred strategy, as evidenced by both our case and another reported case of granulomatous nephritis after BRAF/MEKi treatment.[10] Rechallenge with BRAF/MEKi's after the initial discontinuation may be attempted in patients with SLR, but there are no data to support this strategy. There is only one case of cutaneous sarcoidosis in a patient with melanoma under vemurafenib, in whom the treating physicians selected to discontinue vemurafenib. The eruption resolved completely within three weeks from discontinuation without any further treatment; the patient was treated with ipilimumab, and then sorafenib/bortezomib. Yet a re-challenge with vemurafenib two years after its discontinuation at half the usual dose did not lead to recurrence of the eruption.[12] In conclusion, the decision for re-challenge should be individualized depending on the involved organ and the severity of involvement, as well as the necessity of BRAF/MEKi's for the maintenance of the achieved result.

Treatment shift to ICIs. Most patients developing sarcoidosis from BRAF/MEKi's can continue therapy with BRAF/MEKi's and do not require a treatment shift to ICIs, especially since treatment with ICIs may itself be responsible for SLR, as evidenced by several case reports[49] and review articles.[50] Despite this, in our case of granulomatous nephritis (Case 2), withholding BRAF/MEKi's while continuing treatment with an ICI was an effective, but temporary, measure to maintain the patient's renal function until a definitive diagnosis was made. Eventually, we had to permanently discontinue BRAF/MEKi's while maintaining the ICI. It should also be noted that no cases of ICI-related granulomatous nephritis have been reported so far. In conclusion, a treatment shift to ICIs should be performed in patients with severe involvement, including that related to CNS, renal, or cardiac involvement, while there are still no data on how to manage patients under triple (BRAF/MEKi's and ICI) therapy for melanoma, as was the case of our patient with granulomatous nephritis. A trial of discontinuation and re-challenge with the BRAF/MEKi's can be a useful strategy to define the causative factor before a definitive diagnosis is made and management is initiated.

Follow-up of patients with SLR. Following an effective management of BRAF/MEK-induced SLRs, patients with melanoma and SLR should be closely monitored for both melanoma progression and SLR recurrence. The use of corticosteroids, the temporary or permanent BRAF/MEKi discontinuation, as well as uncertainties on the definitive diagnosis of sarcoidosis, especially after an FNA of lymph nodes showing a sarcoid-like reaction, mandate the close follow-up of the patients for melanoma progression. CT scans and/or PET-CT could be used for that purpose, although it should be borne in mind that sarcoidosis is a PET-avid condition; as a result, a positive PET-CT does not differentiate melanoma from SLR. Despite this, as already mentioned, several imaging patterns tend to be more suggestive of the one over the other condition. A repeat biopsy should be carried out in case of uncertainty. Clinical and imaging testing, as well as special tests depending on the affected organ, should be carried out to follow SLR.

Management of resistant/recurrent disease. Since most patients with melanoma require continuous treatment for their disease, cases of SLR that are resistant to corticosteroids pose a hard-to-solve problem for physicians. Although corticosteroids, along with modifications to melanoma treatment usually suffice to control SLR, other treatments effective in sarcoidosis may be used when steroids are not sufficient. Infliximab, methotrexate, and mycophenolate are all viable options, but there are only a few case reports supporting their use. All three reported cases of sarcoidosis that necessitate the use of immunomodulating drugs other than corticosteroids were ICI-induced.[30,55] In two of these cases, an improvement of the SLR was reported by the authors after corticosteroid, methotrexate, and infliximab administration.

SLR in patients treated in the adjuvant setting. SLR emerging in patients treated in the adjuvant setting for melanoma poses several diagnostic and therapeutic challenges to clinicians. After reaching a definitive diagnosis of BRAF/MEKi-induced SLR in such patients, the threshold for targeted therapy discontinuation is lower. At the same time, the use of corticosteroids should be reserved only for severe cases. Except for the two cases reported in the present article, there are almost no cases of BRAF/MEKi-induced SLRs developing in patients treated in the adjuvant setting. Guidelines for the management of such patients cannot be formulated and the treating physicians should focus on balancing the long-term benefits with the short-term harms of the treatment.

Long-term prognosis of patients with SLR and melanoma. The prognosis of patients exhibiting a BRAF/MEKi-induced SLR has not been thoroughly evaluated, mainly due to the small number of cases reported so far. Despite this, in one report of five patients,[3] the authors noted an overall response rate of 80% in patients developing an SLR under treatment with vemurafenib. In another small case series, the authors report that 43% of patients developing an SLR achieved a CR *versus* 19% for the whole cohort of 63 patients.[8] Similar response rates were documented in a review article of 30 cases of drug-induced SLR in patients with melanoma. The speculated better prognosis of patients with SLR should be interpreted with caution. One plausible explanation of the observed good response and survival rates could be based on the activation of the immune system causing the granulomatous inflammation. If this speculation is proven, it would constitute another reason for not discontinuing the administration of BRAF/MEKi's in patients developing SLRs.

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AA and PD contributed to data acquisition and analysis and wrote the manuscript. GL and EP contributed to data interpretation, CS and DCZ contributed to data acquisition, and HG contributed to data analysis and critically reviewed the manuscript. All authors reviewed the manuscript and approved the submitted version.

Conflict of interest statement

PD reports personal fees from Novartis, Amgen, Janssen, and Roche, outside of the submitted work; HG reports grants and personal fees from BMS and MSD, personal fees from Novartis, Pierre Fabre, Amgen, Sanofi/Regeneron, and Pfizer, outside of the submitted work; the remaining authors report no conflict of interests.

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