

Mediastinal and hilar sarcoid-like reaction in a patient treated with dabrafenib and trametinib for metastatic melanoma: A case report and review of the literature

VANESSA-MELETIA BALA, MARIA MITSOGIANNI,
KONSTANTINOS LASCHOS, EVANGELIA PLIAKOU, EIRINI LAZARIDI,
DIMITRA-IOANNA LAMPROPOULOU and GERASIMOS ARAVANTINOS

2nd Department of Medical Oncology, General Oncology Hospital of
Kifissia 'Agiou Anargyroi', Athens 145 64, Greece

Received December 23, 2021; Accepted March 4, 2022

DOI: 10.3892/mco.2022.2532

Abstract. BRAF/MEK inhibitors are considered standard of care in the treatment of advanced BRAF-mutated malignant melanoma, and have been, in rare cases, associated with granulomatous reactions, mostly limited to skin lesions. The present study reported the case of a patient with metastatic melanoma developing a sarcoid-like reaction manifesting as asymptomatic mediastinal and right hilar lymphadenopathy while on antineoplastic therapy with dabrafenib and trametinib. To the best of our knowledge, this is the first reported case of isolated lymphadenopathy as a manifestation of drug-induced sarcoid-like reaction under dabrafenib and trametinib. Overall, only 17 other cases of granulomatosis have been reported in the literature. Although uncommon, such reactions should be considered in the differential diagnosis of lymph node enlargement, and distinguishing them from tumor progress is important and can be challenging in clinical practice.

Introduction

Metastatic malignant melanoma is a common cause of cancer-related morbidity and mortality (1) and has been historically associated with poor prognosis (2). The

introduction of novel therapies such as immunotherapy and BRAF/MEK inhibition for patients harboring a BRAFV600-mutation have changed drastically the course of the disease and are now considered a standard of care for this population (3).

Approximately 50% of cutaneous melanomas exhibit activating mutations in the B-raf proto-oncogene (BRAF) gene, more commonly in the position V600E. BRAF is part of the mitogen-activated protein kinases (MAPK) pathway and plays a key role in regulation of cellular growth and survival. Activating mutations in the BRAF gene result in continuous downstream activation of the MAPK cascade, including mitogen-activated extracellular signal-regulated kinase (MEK), thus leading to uncontrolled cell proliferation and malignant transformation (4). BRAF inhibition presents significant antitumor activity in BRAF-mutated melanoma, although early development of resistance through alternative MAPK-activating mechanisms is a common clinical problem. Combination of BRAF and MEK inhibition is known to have proven synergic effect and delay the development of acquired resistance (4).

Sarcoidosis is an inflammatory disease of unknown origin characterized by the development of granulomas in various organs, with a possible epidemiological and causal correlation to multiple hematologic and solid malignancies (5). For example, incidence of sarcoidosis in melanoma patients has been estimated at 0.58%, a rate significantly higher in comparison to that of the general population (6). In the last years since the establishment of modern anticancer agents, sarcoidosis and sarcoid-like reactions (SLR) occur more often as a result of treatment, with immunotherapy causing the majority of those cases (7,8). Few cases of drug-induced sarcoidosis and SLR have been described in connection to BRAF inhibitors, alone or combined with MEK inhibitors, and present, in most cases, exclusively as skin reactions (9).

In this report, we discuss the case of a patient developing mediastinal and right hilar lymphadenopathy as the only manifestation of SLR while on dabrafenib and trametinib for metastatic melanoma, and summarize the cases of such granulomatous reactions published in the literature.

Correspondence to: Dr Maria Mitsogianni, 2nd Department of Medical Oncology, General Oncology Hospital of Kifissia 'Agiou Anargyroi', 14 Noufaron and Timiou Stavrou, Nea Kifissia, Athens 145 64, Greece
E-mail: mitsogiannimaria@gmail.com

Abbreviations: SLR, sarcoid-like reaction; SLNB, sentinel lymph node biopsy; CT, computed tomography; EBUS, endobronchial ultrasound bronchoscopy; TBNA, transbronchial needle aspiration

Key words: melanoma, BRAF/MEK inhibitors, dabrafenib, trametinib, sarcoidosis

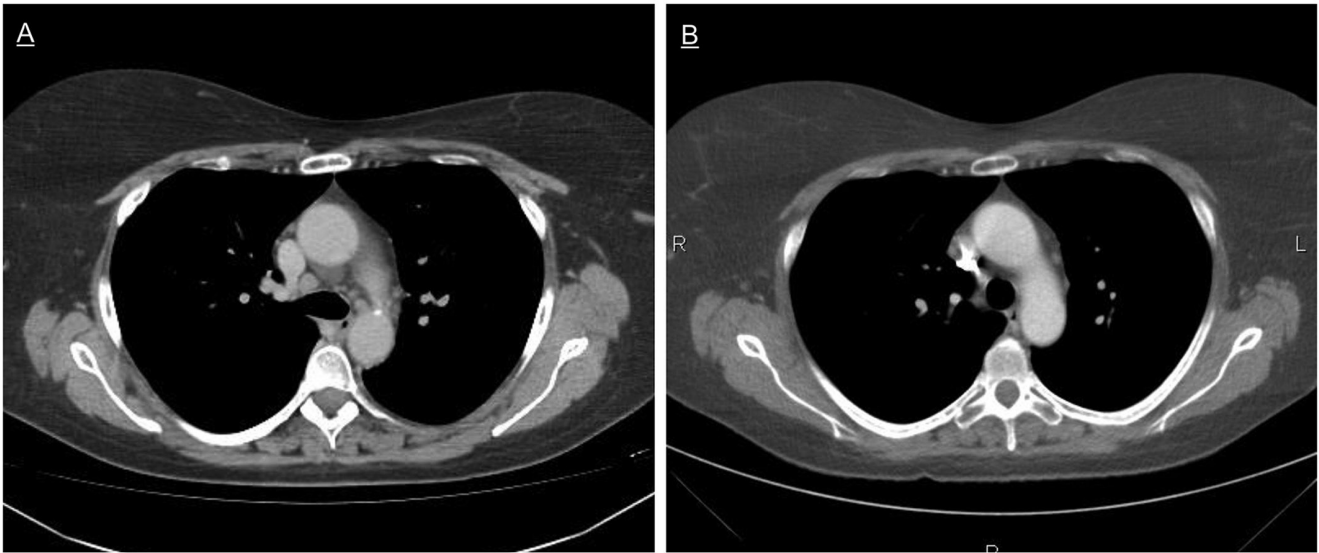


Figure 1. (A) CT scan showing enlarged mediastinal lymph nodes compatible with sarcoidosis. (B) CT scan after 6 months showing spontaneous regression.

Case report

A 55-year-old female, with no significant medical history, no family history of cancer and no current medication, presented in 2016 with a newly detected asymmetric and ulcerated mole in the area of the left scapula. The patient did not report any symptoms, physical examination and laboratory tests revealed no other significant findings.

Wide excision and sentinel lymph node biopsy (SLNB) were performed, leading to the diagnosis of AJCC (7th edition) stage IIB cutaneous melanoma [pT2b (1.5 mm), N0 (SLNB), Clark level 3]. The patient was then scheduled for follow-up. Fifteen months later, physical examination revealed a palpable lymph node of the left axilla. Computed Tomography (CT) scan confirmed lymphadenopathy of the left axilla and mediastinum measuring 1.8 cm in diameter, as well as a 1.7-cm nodule of the left lower lobe. The patient underwent endobronchial ultrasound bronchoscopy (EBUS) with transbronchial needle aspiration (TBNA) and histologic examination of material from the 2L station verified the metastatic nature of the lymphadenopathy along with the presence of BRAFV600E-mutation.

First-line treatment with BRAF/MEK inhibitors dabrafenib 150 mg per os twice daily and trametinib 2 mg per os once daily was initiated on September 2017. Treatment was well tolerated without any adverse events during the first months, and CT scan at 12 months showed complete remission of both the lymphadenopathy and lung nodule. Sixteen months after therapy initiation, CT scan raised the suspicion of disease progression with new marginal mediastinal and right hilar lymphadenopathy of 1.1 cm in short axis (Fig. 1A). The patient had no symptoms, physical and laboratory tests were once again normal. Histopathology obtained through EBUS-TBNA from the stations 4R and 11R showed sarcoid-like non-necrotizing granulomas composed of epithelioid cells, macrophages and T-lymphocytes. Since the patient was asymptomatic, no additional treatment was started and antineoplastic

therapy with dabrafenib/trametinib was continued. The lymphadenopathy regressed spontaneously in the next five months, while the patient remained in complete remission (Fig. 1B). A timeline of all relevant data is presented in Fig. 2.

Discussion

BRAF inhibition has been associated with the development of granulomatous reactions such as sarcoidosis and SLR through immunomodulatory mechanisms that affect the immunosuppressive tumor microenvironment (10). More specifically, patients treated with inhibitors of the MAPK-pathway tend to present increased TNF- α and IFN- γ serum levels (11), which are associated with formation of granulomas. Furthermore, it has been hypothesized that granulomatous reactions could be a paradoxical autoimmune response to BRAF inhibition through CD8⁺ T-cell infiltration and PD-L1 expression (10). Onset of granulomatosis soon after the initiation of treatment with BRAF/MEK inhibitors further supports an etiological relation (9).

In any case, such adverse events remain uncommon. We identified 17 documented cases of histologically confirmed granulomatosis under combined treatment with dabrafenib and trametinib in the literature (10,12-20), which are summarized in Table I. Men and women seem to be almost equally affected (8/17 vs. 9/17), while patient age varies between 19 and 82 years. All but one patient (16/17) suffered from stage IV melanoma, while in one case granulomatosis was diagnosed during adjuvant treatment for stage III disease (20). Time of treatment until the onset of reactions also varies significantly from 1-20 months. Skin lesions were almost universally present (15/17) and the only manifestation in the majority of patients (12/17), while five patients had systemic disease including mediastinal lymph node, kidney, heart, salivary gland, liver and eye involvement. Granulomatous reactions had a generally mild course, with most patients (12/17) reaching a

Table I. Cases of sarcoidosis/sarcoid-like reactions under dabrafenib and trametinib.

First author, year	Sex	Age, years	Stage	Months until onset	Site	Treatment discontinuation	CS	Outcome of SAR/SLR	Melanoma response	(Refs.)
Green, 2013	F	62	IV M1d	9	Skin	No	No	Remission	NR	(12)
	M	72	IV M1b	8	Skin	No	Topical	Remission	NR	
Park, 2014	F	82	IV M1a	2	Skin	No	Topical	Remission	PR	(13)
Jansen, 2015	M	63	IV M1a	18	Skin, kidney	Yes	Systemic	Remission	CR	(14)
Winkler, 2018	M	46	IV M1b	2	Myocardium	No	No	Death	CR	(15)
Rueda-Rueda, 2018	F	39	IV	2	Uvea	Yes	Systemic + Topical	Remission	PD	(16)
Dimitriou, 2018	M	19	IV M1c	1	Skin	No	Topical	Remission	CR	(10)
Korman, 2018	F	49	IV M1b	12	Skin	No	No	Progress	CR	(17)
Giet, 2019	M	30	IV M1c	4	Skin	NR	Topical	Stable	NR	(18)
Huynh, 2020	F	61	IV M1c 1	8	Skin	No	No	Remission	PD	(19)
	F	77	IV M1a 0	20	Skin	No	Topical	Remission	CR	
	M	45	IV M1d 0	2	Skin, salivary glands, mediastinal lymph nodes	No, dose reduction	No	Remission	PD	
	F	49	IV M1c 0	15	Skin	No, dose reduction	Topical	Relapse	CR	
	F	66	IV M1a 0	2	Skin	No	Topical	Remission	PD	
	M	57	IV M1b 0	6.5	Skin	No	Topical	Remission	CR	
	F	82	IV M1b 1	11	Skin	No, dose reduction	Topical	Stable	PD	
Boutros, 2020	M	38	III	3	Skin, liver, uvea, mediastinal lymph nodes	Yes	Topical	Remission	Relapse-free	(20)

M, male; F, female; NR, not reported; CS, corticosteroids; SAR, sarcoidosis; SLR, sarcoid-like reaction; PR, partial remission; CR, complete remission; PD, progressive disease.

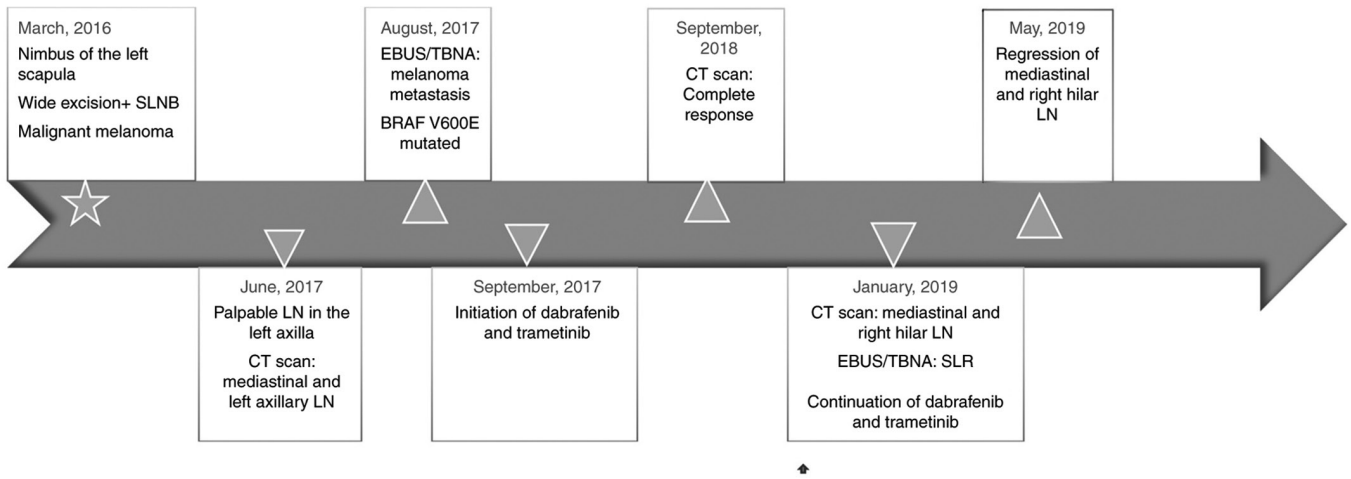


Figure 2. Timeline of the course of disease and treatment. SLNB, sentinel lymph node biopsy; CT, computed tomography; EBUS, endobronchial ultrasound bronchoscopy; TBNA, transbronchial needle aspiration; LN, lymphadenopathy.

remission: discontinuation of dabrafenib and trametinib was necessary in three cases, topical corticosteroids in eleven and systemic corticosteroid treatment in two. One patient died due to granulomatous myocarditis before receiving any specific treatment (15). Melanoma response was more diverse: nine patients responded to BRAF/MEK inhibition and another five progressed.

In accordance with, to date, published data, SLR in our case had benign clinical behavior and resolved without special treatment. However, skin lesions were absent and mediastinal or hilar lymphadenopathy was the only manifestation. To our knowledge, this is the first documented case of isolated lymphadenopathy due to SLR in a patient receiving the combination of dabrafenib and trametinib. Other BRAF-inhibitors such as vemurafenib, with or without cobimetinib, have also been associated with granulomatous reactions (13,21-23), but isolated mediastinal or hilar lymphadenopathy has not been described with these agents either. This observation raises the question if SLR without skin involvement is an extremely rare entity under BRAF/MEK inhibition or if it could sometimes be mistaken for progressive disease in clinical practice. In any case, it is reasonable to acquire tissue biopsy in case of newly detected lymphadenopathy in order to establish a definite diagnosis (9).

Due to the small number of documented cases and the lack of prospective studies, many questions remain unanswered. It is not known which patients develop drug-induced granulomatous reactions, what is the optimal therapy, if any, and in which cases discontinuation of BRAF/MEK inhibition is necessary (9). It has been suggested that treatment-related sarcoidosis is associated with better efficacy of BRAF inhibitors (24), but data is very limited.

In summary, granulomatous reactions in patients receiving dabrafenib and trametinib for advanced melanoma are rare, usually mild adverse events. Our case describes the uncommon entity of SLR with isolated mediastinal and hilar lymphadenopathy and underlines the importance of differential diagnosis from tumor progress. Further research is needed in order to define the optimal management of these patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

VMB and MM treated the patient, designed the study and wrote the manuscript. KL treated the patient, analyzed the findings and critically revised the manuscript. EP, EL and DIL analyzed and interpreted the findings, and reviewed and edited the manuscript. GA made substantial contributions to conception and design, and reviewed the manuscript. VMB and MM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2021. *CA Cancer J Clin* 71: 7-33, 2021.

2. Rubin KM and Lawrence DP: Your patient with melanoma: Staging, prognosis, and treatment. *Oncology (Williston Park)* 23 (Suppl 8): S13-S21, 2009.
3. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R and Keilholz U; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org: Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 30: 1884-1901, 2019.
4. Mandalà M and Voit C: Targeting BRAF in melanoma: Biological and clinical challenges. *Crit Rev Oncol Hematol* 87: 239-255, 2013.
5. El Jammal T, Pavic M, Gerfaud-Valentin M, Jamilloux Y and Sève P: Sarcoidosis and cancer: A complex relationship. *Front Med (Lausanne)* 7: 594118, 2020.
6. Seve P, Schott AM, Pavic M, Broussolle C, Gilis L and Thomas L: Sarcoidosis and melanoma: A referral center study of 1,199 cases. *Dermatology* 219: 25-31, 2009.
7. Cohen Aubart F, Lhote R, Amoura A, Valeyre D, Haroche J, Amoura Z and Lebrun-Vignes B: Drug-induced sarcoidosis: An overview of the WHO pharmacovigilance database. *J Intern Med* 288: 356-362, 2020.
8. Gkiozos I, Kopitopoulou A, Kalkanis A, Vamvakaris IN, Judson MA and Syrigos KN: Sarcoidosis-like reactions induced by checkpoint inhibitors. *J Thorac Oncol* 13: 1076-1082, 2018.
9. Rubio-Rivas M, Moreira C and Marcoval J: Sarcoidosis related to checkpoint and BRAF/MEK inhibitors in melanoma. *Autoimmun Rev* 19: 102587, 2020.
10. Dimitriou F, Frauchiger AL, Urosevic-Maiwald M, Naegeli MC, Goldinger SM, Barysch M, Franzen D, Kamarachev J, Braun R, Dummer R and Mangana J: Sarcoid-like reactions in patients receiving modern melanoma treatment. *Melanoma Res* 28: 230-236, 2018.
11. Wilmott JS, Haydu LE, Menzies AM, Lum T, Hyman J, Thompson JF, Hersey P, Kefford RF, Scolyer RA and Long GV: Dynamics of chemokine, cytokine, and growth factor serum levels in BRAF-mutant melanoma patients during BRAF inhibitor treatment. *J Immunol* 192: 2505-2513, 2014.
12. Green JS, Norris DA and Wisell J: Novel cutaneous effects of combination chemotherapy with BRAF and MEK inhibitors: A report of two cases. *Br J Dermatol* 169: 172-176, 2013.
13. Park JJ, Hawryluk EB, Tahan SR, Flaherty K and Kim CC: Cutaneous granulomatous eruption and successful response to potent topical steroids in patients undergoing targeted BRAF inhibitor treatment for metastatic melanoma. *JAMA Dermatol* 150: 307-311, 2014.
14. Jansen YJ, Janssens P, Hoorens A, Schreuer MS, Seremet T, Wilgenhof S and Neyns B: Granulomatous nephritis and dermatitis in a patient with BRAF V600E mutant metastatic melanoma treated with dabrafenib and trametinib. *Melanoma Res* 25: 550-554, 2015.
15. Winkler JK, Buder-Bakhaya K, Ellert E, Herpel E, Martens UM, Enk A and Hassel JC: Acute heart failure as a result of granulomatous myocarditis: Case report on a patient with metastatic melanoma treated with dabrafenib and trametinib. *J Eur Acad Dermatol Venereol* 32: e31-e32, 2018.
16. Rueda-Rueda T, Sánchez-Vicente JL, Moruno-Rodríguez A, Molina-Socola FE, Martínez-Borrego AC and López-Herrero F: Uveitis and serous retinal detachment secondary to systemic dabrafenib and trametinib. *Arch Soc Esp Oftalmol (Engl Ed)* 93: 458-462, 2018 (In English, Spanish).
17. Korman AM, Nisar MS and Somach SC: Subclinical granulomas in benign skin lesions heralding the onset of BRAF and MEK inhibitor-associated granulomatous dermatitis in a patient with metastatic melanoma. *JAAD Case Rep* 4: 722-724, 2018.
18. Giet G, Lebas E, Rorive A, Arrese JE and Nikkels AF: Granulomatous reactions from tattoos following BRAF inhibitor therapy. *Case Rep Dermatol* 11: 101-107, 2019.
19. Huynh S, Lheure C, Franck N, Goldman-Lévy G, Aractingi S, Dupin N, Kramkimel N and Guégan S: Induced sarcoid-like reactions in patients with metastatic melanoma treated with dabrafenib and trametinib: A monocentric retrospective study. *Melanoma Res* 30: 317-320, 2020.
20. Boutros A, Schiavi C, Cecchi F, Spagnolo F, Guadagno A, Tanda ET, Giusti F, Murdaca G and Queirolo P: Case report: Immune-related toxicity during adjuvant treatment with BRAF plus MEK inhibitors in a melanoma patient. *Front Immunol* 11: 579523, 2020.
21. Adam A, Thomas L, Bories N, Zaharia D, Balme B, Freymond N and Dalle S: Sarcoidosis associated with vemurafenib. *Br J Dermatol* 169: 206-208, 2013.
22. Hui Ong EL, Sinha R, Jmor S and Fearfield L: BRAF inhibitor-associated granulomatous dermatitis: A report of 3 cases. *Am J Dermatopathol* 41: 214-217, 2019.
23. Assan F, Schlemmer F, Assie JB, Mahevas M, Sustronck P, Ortonne N, Velter C, Fardet L and Zehou O: Atypical systemic sarcoid-like granulomatosis in two patients treated with BRAF and MEK inhibitors. *Eur J Dermatol* 29: 556-557, 2019.
24. Lheure C, Kramkimel N, Franck N, Laurent-Roussel S, Carlotti A, Queant A, Goldwasser F, Avril MF and Dupin N: Sarcoidosis in patients treated with vemurafenib for metastatic melanoma: A paradoxical autoimmune activation. *Dermatology* 231: 378-384, 2015.