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Case Report

A Case of Pulmonary Sarcoidosis during First-Line Targeted Therapy with Dabrafenib Plus Trametinib in *BRAF* V600E-Mutated Metastatic Melanoma

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Keywords
Melanoma · Targeted therapy · Dabrafenib · Trametinib · Sarcoidosis · Immune-mediated event

Abstract
BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) exert a cytotoxic and immune-mediated effect on metastatic melanoma. The immune-mediated mechanism can lead to some adverse events, including panniculitis, erythema, keratitis, vitiligo-like lesions, or, more rarely, sarcoid-like skin reactions. In particular, sarcoidosis-related manifestations during melanoma treatment are characterized mainly by skin involvement and are seldom associated with chest or lymph node lesions. Overall, managing these adverse events can be very challenging from the diagnostic and therapeutic points of view. We present a case of pulmonary sarcoidosis; it is the first without skin involvement and initially only with lung presentation, diagnosed during treatment with BRAFi and MEKi for metastatic cutaneous melanoma. After about 2 years of

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treatment, with an oncological complete response, a histologically confirmed form of pulmonary sarcoidosis was diagnosed and initially interpreted as tumor progression. Sarcoidosis has always remained asymptomatic. After progression in the thorax and supraclavicular lymph nodes, steroid therapy with prednisone was instituted with total remission of the signs of disease. The targeted therapy has never been interrupted, and the patient still shows a complete response. This clinical case suggests that rare immune-mediated events, such as pulmonary sarcoidosis, should be considered during targeted therapy for metastatic melanoma and not only during treatment with immune checkpoint inhibitors. It also suggests that the interruption of targeted treatment should be accurately considered based on the expected risks or benefits since such immune-mediated events may have low clinical impact.

Introduction

A combination of BRAF and MEK inhibitors (BRAFi and MEKi), such as dabrafenib and trametinib, represents the standard of care in metastatic or locally advanced *BRAF* V600-mutated melanoma. At present, three combinations of BRAFi and MEKi have been approved worldwide: vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib; they are characterized by similar efficacy [1–3].

BRAFi and MEKi exert a cytotoxic and immune-mediated effect on metastatic melanoma [4, 5]. The immune-mediated mechanism can lead to some adverse events, including panniculitis, erythema, keratitis, vitiligo-like lesions, or, more rarely, sarcoid-like skin reactions [6, 7]. In particular, sarcoidosis-related manifestations during melanoma treatment are characterized mainly by skin involvement and are seldom associated with chest or lymph node lesions [8].

We present a case of pulmonary sarcoidosis diagnosed during targeted treatment with BRAFi and MEKi, dabrafenib and trametinib, for metastatic cutaneous melanoma. To our knowledge, this is the first case of pulmonary sarcoidosis without skin involvement and initially only with lung presentation during BRAFi and MEKi.

Case Presentation

In January 2015, a 45-year-old patient without relevant clinical history underwent a skin biopsy for a pigmented nevus localized on the back, resulting in a diagnosis of nodular melanoma with the presence of *BRAF* V600E mutation. After 1 month, surgical radicalization with sentinel lymph node biopsy was performed, showing pT4bN1a stage. Axilla nodal dissection was completed in May 2015, without any evidence of disease. Brain computerized tomography scan (CT scan) and fluorodeoxyglucose (FDG)-PET were negative for distant metastasis; therefore, the patient was referred to clinical and radiological follow-up every 3 months. In October 2017, follow-up imaging revealed left axillary lymphadenopathy with a diameter of 14 × 12 mm and two pulmonary micronodules. First-line treatment with dabrafenib 300 mg/day and trametinib 2 mg/day was started, leading to a complete response; tolerability was excellent, without any dose modifications. In July 2019, a total body CT scan documented the development of two pulmonary micronodules in the left lower lobe (8 mm and 6 mm) and the presence of several mediastinal lymphadenopathies (max dimensions 20 × 15 mm) (Fig. 1a). FDG-PET was performed and revealed a small hypercaptation area in the left lung. After a multidisciplinary discussion, we decided to perform a pulmonary metastasectomy with nodal removal, with

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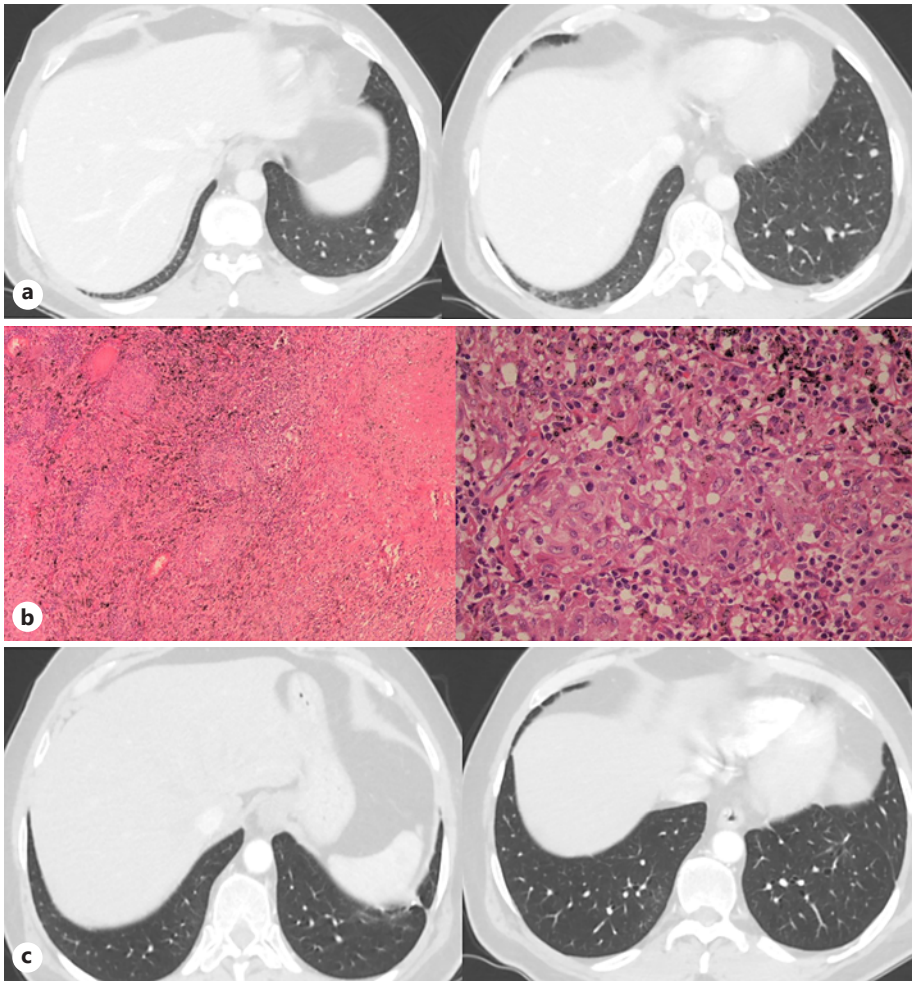

Fig. 1. Imaging of the patient. **a** Pulmonary bilateral micronodules documented by CT scan (July 2019). **b** "Macro"- and "micro"-histopathologic features of sarcoidosis. **c** Regression of micronodules documented by CT scan (February 2021).

diagnostic and therapeutic intent. Surgery was performed in September 2019. Histological examination showed the presence of granulomas constituted by epithelial and giant multinucleated cells, Langhans cells, without any sign of necrosis (Fig. 1b). These findings were consistent with the presence of sarcoidosis. Pulmonary function was normal, and the alveolar-capillary diffusion of CO was within limits. Due to the lack of sarcoidosis-related symptoms, a pulmonologist examined the patient and decided not to treat him. Given the response and the good tolerability, targeted therapy was continued.

In August 2020, the FDG-PET showed hypercaptation in almost all the mediastinal nodal stations, some subphrenical nodes, sovraclavicular nodes, and the lower lobe of the left lung. A biopsy in the left supraclavicular lobe was performed to exclude disease progression, which confirmed the inflammatory nature of the adenopathies compatible with pulmonary sarcoidosis; no malignant tumor cells were present. The patient presented as almost asymptomatic with only mild dyspnea on exertion; no cough, osteoarticular pain, or fever was reported. No abnormalities of liver function or inflammation indices were disclosed; normal angiotensin-converting enzyme levels were measured. Systemic steroids were given to the patient, prednisone 50 mg/daily for 2 weeks, then 25 mg/daily for 2 weeks, with complete recovery and good tolerability.

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At the time of the drafting of this article, after more than 3 years of therapy, the patient still presents an oncological complete response. No pulmonary symptoms or signs of sarcoidosis are present (Fig. 1c).

Discussion

Sarcoidosis is a multisystem granulomatous disease. This condition is associated with melanoma and can be induced in melanoma patients with anti-PD-1 agents [8–10]. It is unclear whether the development of sarcoidosis in these patients represents an autoimmune disease, which was not evident until the onset of melanoma, or rather is a marker of oncologic response. To date, associations of long clinical benefit and development of sarcoidosis in patients treated with targeted therapy are not known. In a recent systematic review, specific skin involvement is the most common manifestation of sarcoidosis in patients on BRAFi/MEKi (papules); chest X-ray stage 0 (no lesions) at diagnosis is usually reported in patients on BRAFi/MEKi, while stage I–II is predominant in the CTLA-4 and PD-1 patients [8].

Boutros et al. [9] reported a case of systemic sarcoidosis with skin involvement during adjuvant treatment with dabrafenib plus trametinib; this patient presented skin and uveal granulomatosis while mediastinal reactive lymph nodes were documented at the thorax CT scan. Moreover, fever and transaminitis were present. The adjuvant treatment was permanently discontinued after 6 months because the symptoms relapsed with a dose reduction. After discontinuation, the patient was asymptomatic without any signs of melanoma relapse after 1 year of follow-up.

We present the first case of pulmonary and subsequently lymph nodes sarcoidosis with histopathologic confirmation without skin lesions developed during BRAFi/MEKi treatment. The course of sarcoidosis was asymptomatic and never required interruptions of oncological treatment. Remission of melanoma was maintained.

Awareness of the risk of developing sarcoidosis and its radiological features can help avoid misdiagnosis of disease progression and unnecessary treatment interruptions. A multidisciplinary team involving a pulmonologist, radiologist, nuclear, and oncologist is crucial for interpreting the clinical picture and optimizing patient care. Of note, interruption of targeted therapy in metastatic melanoma is not advisable, even if in the presence of complete response [11].

Conclusion

Rare immune-mediated events, such as pulmonary sarcoidosis, should be considered during targeted therapy for metastatic melanoma and not only during or following ICIs, even in the absence of skin manifestations. In these cases, the interruption of targeted treatment should be accurately considered based on the expected risks or benefits, since such immune-mediated events may have low clinical impact. Further clinical investigations and prospective data are needed to better understand the interaction between the immunological system and targeted therapies with BRAFi and MEKi, particularly to identify immune response activation biomarkers that may correlate with treatment response.

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Statement of Ethics

The participant signed an informed consent form for publication of the details of the medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines as this is not about clinical research or study. It is about day-to-day management of a cancer patient based on standard treatment protocol.

Conflict of Interest Statement

None of the authors declared conflicts of interest.

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Author Contributions

Study design: Maria Chiara Tronconi; data collection and interpretation: Maria Chiara Tronconi, Arianna Marinello, Alessandra Solferino, Susanna Grimaudo, Michele Ciccarelli, Sofia Manara, Luca Cozzaglio, Luca Mancini, Riccardo Borroni, and Armando Santoro; manuscript writing: Maria Chiara Tronconi; manuscript editing and approval to submit: Maria Chiara Tronconi, Arianna Marinello, Alessandra Solferino, Susanna Grimaudo, Michele Ciccarelli, Sofia Manara, Luca Cozzaglio, Luca Mancini, Riccardo Borroni, and Armando Santoro.

Data Availability Statement

All data analyzed in this case report are included in this article and/or its figures. Further data may be made available upon reasonable request to the corresponding author.

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