Cutaneous Granulomatous Eruption and Successful Response to Potent Topical Steroids in Patients Undergoing Targeted BRAF Inhibitor Treatment for Metastatic Melanoma

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In patients with advanced melanoma, mean survival time is 6 to 9 months and the 3-year survival rate is 10% to 15% historically. BRAF mutations are found in approximately 40% to 60% of melanomas, 90% of which possess a V600E point mutation.1,2 Vemurafenib, which is US Food and Drug Administration (FDA) approved for metastatic melanoma treatment, targets the driver oncogenic mutation BRAFV600E, a mediator in the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) signaling pathway that leads to cell proliferation and differentiation.2 Patients treated with vemurafenib have been reported to have a substantial overall response rate (53%) and improved median overall survival rate (15.9 months).3 However, responses to therapy may last less than 1 year, and mechanisms of resistance have recently been elucidated.4 Ongoing clinical trials for patients with the BRAFV600E mutation include the use of MEK inhibitors together with targeted BRAF inhibition to address acquired resistance to BRAF inhibitors alone. Our 2 patients illustrate granulomas after the initiation of targeted BRAF inhibitor therapy.

Report of Cases

Case 1
A woman in her 80s received a diagnosis of a 2.25-mm Breslow depth/Clark level IV nonulcerated superficial-spreading melanoma with 5 mitotic figures per high-power field on her right dorsal foot. She underwent a wide local excision and a sentinel lymph node biopsy that was negative for melanoma, and 1.5 years later, she presented with multiple pink and light brown papules 1 to 5 mm in diameter on her right leg, proximal and distal to the knee (Figure 1A). A punch biopsy confirmed metastatic melanoma, which was found to be positive for the BRAFV600E mutation, and she had no other disease on additional staging scans. The patient’s disease was staged as M1a stage IV melanoma given her distant subcutaneous disease, and she consented to and began treatment as a participant in a clinical trial of targeted BRAF inhibitor dabrafenib (GSK2118436; 75-mg oral pills twice daily) and MEK inhibitor trametinib (GSK1120212; 2-mg oral pills daily) therapy. After 1 month of treatment, the patient...
had fewer and less pronounced papules in the area of her disease, demonstrating clinical response to treatment. However, after approximately 2 months of treatment, the patient presented with numerous new erythematous and violaceous, firm, 1 to 2-mm papules, as well as an erythematous, indurated 5-cm plaque around the areas of her known subcutaneous disease (Figure 1B). On the basis of the clinical appearance and distribution of the lesions, the eruption was concerning for progression of metastatic melanoma and her treatment was put on hold. Two 3-mm punch biopsies were performed, 1 biopsy on the right anterior lower leg revealing a perifollicular granulomatous inflammation (Figure 2) and the second biopsy on the right medial thigh revealing granulomatous inflammation surrounding a focus of melanoma cells highlighted by melanoma antigen recognized by T cells (MART-1) and microphthalmia transcription factor (MITF) immunostains (Figure 3).

The patient was instructed to apply clobetasol ointment twice daily under occlusion with plastic wrap. One week later, the patient had near-complete resolution of her new eruption revealing continued improvement of her in-transit disease, and the BRAF inhibitor and MEK inhibitor protocol treatment was resumed. After 2 weeks of topical steroid treatment, the eruption had resolved completely, and clobetasol treatment was discontinued (Figure 1C). The area of subcutaneous disease remains improved, and the patient continues to receive targeted treatment at this time after 9 months of therapy.

**Case 2**

A man in his 70s with a history of stage III melanoma of the right lower extremity developed a recurrence in the right groin 9 years later and underwent 1 year of high-dose interferon therapy. Five years later, he developed an enlarging right subpleural nodule with 3 enlarged hilar nodes, which on surgical resection was found to be consistent with metastatic melanoma. The patient initially consented and enrolled in a clinical trial of combined temozolomide and
PARP (poly adenosine diphosphate ribose polymerase) inhibitor therapy, and the study medication therapy was stopped after 6 months because of progression of disease. His metastatic melanoma was determined to be positive for the \textit{BRAF}^{V600E} mutation, and he began treatment with vemurafenib on clinical trial (RO5185426; 960-mg oral pills twice daily). After 5 months of treatment, he presented with multiple asymptomatic scattered erythematous and violaceous papules scattered over his bilateral upper and lower extremities. A 4-mm punch biopsy of his right leg revealed granulomatous dermatitis with focal necrosis (Figure 4). The rash worsened over the next 3 weeks, during which the study protocol was discontinued because of progression of melanoma seen on repeated positron emission tomographic/computed tomographic scan. A complete spontaneous resolution of cutaneous findings was observed approximately 3 weeks after the discontinuation of vemurafenib treatment while the patient was receiving supportive care only. He was subsequently transitioned to a regimen of ipilimumab for 6 months and then to a clinical trial of sorafenib/bortezomib for 8 months and experienced progression of disease with both study therapies. Approximately 2 years after first initiating vemurafenib treatment, the patient began rechallenge with vemurafenib (half the usual dose, ie, 480-mg dose twice daily due to general symptoms), and he did not have any recurrent granulomatous eruptions. However, his disease progressed again, and after receiving palliative therapy, he died almost 5 years after his diagnosis of stage IV disease.

Discussion

Common adverse effects of targeted \textit{BRAF} inhibitors include arthralgias, fatigue, nausea, and diarrhea; cutaneous effects reported include photosensitivity, follicular hyperkeratotic and/or keratosis pilaris-like rash, verruciform hyperkeratosis, squamous cell carcinomas (SCCs), keratoacanthomas, palmar-plantar erythrodysesthesia, erythema nodosum, and alterations of nevi.\textsuperscript{5} Squamous cell carcinomas and keratoacanthomas have been reported to develop in approximately 19% to 26% of patients within 2 to 36 weeks of the treatment.\textsuperscript{6} Squamous cell carcinomas in patients treated with vemurafenib have increased prevalence of \textit{HRAS} mutations compared with sporadic SCC,\textsuperscript{7} which suggests a paradoxical activation of the MAPK signaling pathway induced by \textit{BRAF} inhibitors, potentially by priming wild-type RAF to activate the MAPK pathway, particularly in the presence of an activating \textit{RAS} mutation.\textsuperscript{8} The addition of an inhibitor of MEK, a kinase downstream of RAF, to targeted \textit{BRAF} inhibition may mitigate tumor resistance and has been shown to reduce cutaneous adverse effects of \textit{BRAF} inhibition, including a reduction in SCC.\textsuperscript{4,6} Although interferon and PARP inhibitors, which were used to treat the patient in case 2 prior to vemurafenib, are also known to induce immunomodulatory changes, the timing of onset of the granulomatous eruption after initiation of vemurafenib treatment and cessation of eruption after stopping the drug treatment suggests a correlation between granulomas and \textit{BRAF} inhibition. To our knowledge, granulomatous erup-
Granulomas are a pattern of inflammation defined as a collection of epithelioid histiocytes surrounded by giant cells and lymphocytes that develop during the body's attempt to enclose foreign bodies or inciting agents. Tuberculosis, fungal infections, foreign material, cat-scratch disease, sarcoidosis, and Crohn disease are examples of infections and diseases with granulomatous reactions. The granulomatous inflammation is initiated by antigen-presenting cells, which activate T cells to secrete interleukin 2 (IL-2) and interferon γ, which activates additional T cells and macrophages, respectively. The activated macrophages transform into epithelioid histiocytes and giant cells.

Several neoplasms, such as renal cell carcinoma and many others, including malignant lymphomas, renal cell carcinoma, nasopharyngeal carcinoma, seminoma of the testes, ovarian dysgerminoma, and melanoma have had reported associations with granulomas. Sarcoidal granulomatous reactions have also been described in patients with Hodgkin disease, non-Hodgkin lymphoma, and carcinomas. Although the pathophysiologic mechanism of granulomatous responses to neoplasms is unknown, it is hypothesized that the granulomas are caused by an aberrant cytokine release by tumor cells or may represent a nonspecific host response to the tumor. Interestingly, 2 reports have observed favorable clinical outcomes including fewer relapses and longer survival among patients with Hodgkin disease who developed granulomas, which was described as an unspecified “host response.” Similarly, Baselmans and colleagues reported regression of solid SL2 lymphosarcoma by a granulomatous inflammatory reaction, speculated to be IL-2 mediated.

There is limited information in the literature regarding an association of granulomas and melanoma. In 1997, Robert and colleagues reported granulomatous reactions in 7 patients with melanoma: 3 patients with true sarcoïdosis, 1 patient with tumor-associated granuloma at regional lymph node, and 3 patients with atypical tumor-associated granulomatoses believed to represent melanoma metastases. Tsunoda and colleagues reported a case of malignant melanoma associated with a cutaneous sarcoïdoid reaction, postulated to result from a T-cell-mediated immune response to a tumor. The sarcoïdoid granulomas resolved with treatment of the melanoma. Cutaneous and pulmonary sarcoïdosis have been associated with interferon α therapy for melanoma, where authors hypothesize a similar tumor cytokine–induced and antigen-induced immune response as the pathogenesis of the reaction, although it is not clear whether the granulomas are an adverse effect of interferon treatment or tumor.

Although targeted BRAF inhibitors are not known to have activating effects on the immune system, we speculate that the granulomatous eruption during therapy may represent an immune response or activation against targets on melanoma cells perhaps unveiled by treatment. It is interesting that the second biopsy in case 1 revealed melanoma cells central to the granulomatous reaction (Figure 3B), suggesting that the reaction was incited by the melanoma cells. It is possible that such a response may represent a positive therapeutic response to targeted BRAF inhibition. This hypothesis poses an interesting clinical question: is it beneficial or necessary to treat this granulomatous cutaneous response in the setting of BRAF inhibitor therapy? Clinical trial protocols call for holding therapy in the setting of new-onset rash, and treatment of new-onset rashes during therapy is standard. It is possible that the granulomatous cutaneous reaction represents a positive therapeutic sign and may not need to be treated. This hypothesis requires further evaluation. The patient in case 1 continues to do well as a complete responder according to response evaluation criteria in solid tumors more than 1 year after diagnosis of metastatic disease. Although in case 2, the patient’s disease progressed after the onset of his granulomatous rash, it is still possible that his rash represented a positive response to treatment with vemurafenib, whether via a local response if there were cutaneous microscopic disease vs systemic response to his visceral disease. The fact that he did not have the same rash on rechallenge of the drug is especially interesting in that this would argue against a drug-induced hypersensitivity-like reaction. It is notable that the patient survived almost 5 years after receiving a diagnosis of stage-IV disease.

In case 1, the patient’s granulomatous eruption was treated as a noninfectious granulomatous eruption with clobetasol ointment under occlusion, which caused rapid improvement within days. The present case report, to our knowledge, is the first to describe granulomatous eruptions in the setting of targeted BRAF inhibitor therapy. We propose that granuloma formation represents immune activation toward possible melanoma regression. The cutaneous changes can be treated with potent topical steroids, thereby preventing any unnecessary discontinuation of therapy. Additional studies are warranted to explore the clinical importance of granulomatous eruptions in targeted BRAF inhibitor therapy and potential positive therapeutic outcomes. Given the FDA approval of vemurafenib as a first-line treatment for metastatic melanoma and ongoing clinical trials with other targeted BRAF inhibitors, clinicians should be aware of this possible cutaneous reaction and treatment option to help optimize patient management.

ARTICLE INFORMATION

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Case Report/Case Series Research

REFERENCES


