

# Cobimetinib- and vemurafenib-induced granulomatous dermatitis and erythema induratum: A case report

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## Abstract

Metastatic melanoma is an aggressive malignancy. Survival can be increased with the combination of BRAF and MEK inhibition. BRAF inhibitor-induced cutaneous toxicities can be attenuated with MEK inhibition. Here, we describe the first reported case of a patient with metastatic melanoma who developed granulomatous dermatitis and erythema induratum when treated with combination BRAF (vemurafenib) and MEK inhibitor (cobimetinib) therapy and discuss the clinical features and management of dermatologic side-effects secondary to BRAF +/- MEK inhibition.

## Keywords

Cobimetinib, vemurafenib, granulomatous dermatitis, erythema induratum

## Introduction

Metastatic melanoma is an aggressive malignancy with a 5-year survival <10%.<sup>1</sup> New drug developments are exploiting the constitutively activated BRAF mutations found in 40%–60% of melanoma patients.<sup>2–4</sup> The BRIM-3 (BRAF Inhibitors in Melanoma 3) trial showed the BRAF inhibitor vemurafenib increased median overall survival (mOS) when compared to dacarbazine.<sup>5</sup> When vemurafenib is combined with the MEK inhibitor cobimetinib, median progression-free survival (mPFS) significantly increased compared with vemurafenib alone.<sup>6</sup> Similar results were observed in the COMBI-d trial evaluating the BRAF inhibitor dabrafenib with MEK inhibitor trametinib.<sup>7</sup>

Patients receiving BRAF inhibitors can develop a variety of cutaneous toxicities, with malignant skin lesions the most concerning.<sup>8–13</sup> Combining BRAF plus MEK inhibitors has led to a global reduction in all cutaneous toxicities compared to BRAF inhibition alone.<sup>6,14–16</sup> Here, we describe the first reported case of a patient with metastatic melanoma who developed granulomatous dermatitis, and later erythema induratum, when treated with both vemurafenib and cobimetinib.

## Case report

Our 37-year-old male patient underwent resection of a T4b N1a malignant melanoma in 2012. After 4 months of adjuvant interferon, he developed biopsy-proven BRAF V600E

mutation recurrence at his scar and two pulmonary metastases, resected in April 2013. In September 2013, he developed a subcutaneous metastasis, as well as solitary pulmonary and left adrenal metastases. In November 2013, he began treatment on a clinical trial with vemurafenib; subsequent unblinding revealed he also received cobimetinib.

After 7 months of treatment, he developed symptomatic Grade-2 subretinal fluid and central serous retinopathy, necessitating a 3-week treatment interruption and subsequent vemurafenib dose-reduction. In December 2014, he developed a Grade-1 non-pruritic painful rash on both arms, progressing to Grade-3 rash covering over 50% of his body at follow-up 4 weeks later. Skin biopsy showed a vemurafenib-induced granulomatous dermatitis with multiple non-caseating granulomas in the superficial and deep dermis (Figure 1(a) and (b)). Treatment was held for 4 weeks and his rash reduced to Grade 1. Vemurafenib was reintroduced with

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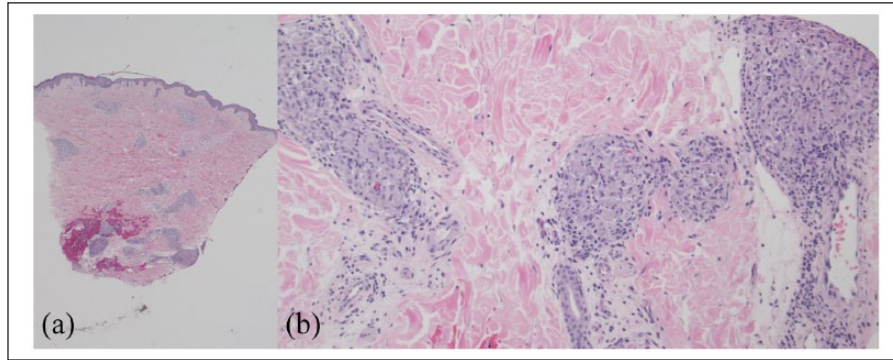
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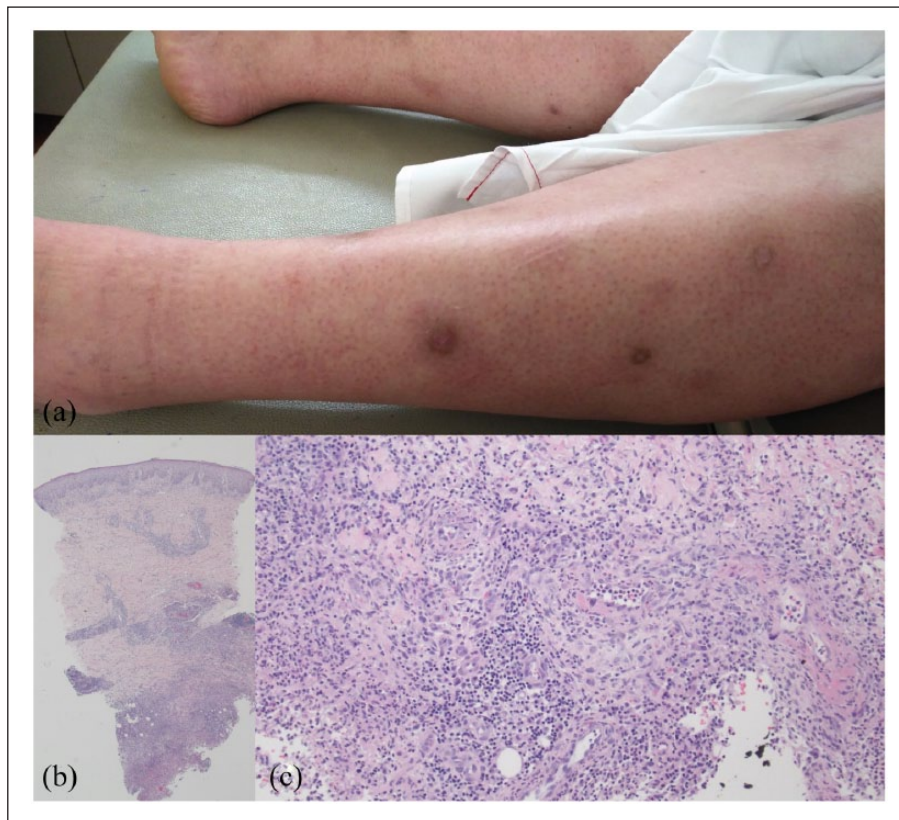
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**Figure 1.** Patient developed non-pruritic painful rash on both arms after 13 months of combination vemurafenib and cobimetinib. Skin punch biopsies with haematoxylin and eosin stain at (a) 20 $\times$  magnification and (b) 100 $\times$  magnification: granulomatous dermatitis with multiple non-caseating granulomas in superficial and deep dermis.



**Figure 2.** (a) At 26 months of combination vemurafenib and cobimetinib, the patient developed non-pruritic and non-painful lesions on his legs. Skin punch biopsies with haematoxylin and eosin stain at (b) 20 $\times$  magnification and (c) 100 $\times$  magnification: neutrophilic lobular panniculitis with vasculitis known as erythema induratum.

a second dose-reduction and cobimetinib with one dose-reduction. By April 2015, he had no measurable disease on imaging.

In January 2016, he presented with left anteriolateral shin lesions. Ultrasound was non-diagnostic and the lesions spontaneously resolved while on treatment. He subsequently developed four large non-painful, non-pruritic, purple-coloured

lesions on his legs (Figure 2(a)) in May 2016. Biopsies of these lesions revealed neutrophilic lobular panniculitis with vasculitis, known as erythema induratum (Figure 2(b) and (c)). Vemurafenib and cobimetinib were held for 4 weeks and his lesions resolved. Upon restarting treatment, he again developed non-painful lesions on his shins, which would spontaneously resolve and intermittently recur without drug discontinuation;

occasional use of clobetasol topical steroid did not appear to have clinical impact. Treatment was held one additional time due to the development of a nodule on his foot that made shoes uncomfortable.

In July 2016, cobimetinib was further dose-reduced due to treatment-related fatigue. While on this lowest dose level of both drugs, he developed bilateral increased intra-ocular pressure in March 2017, which resolved with brimonidine/timolol eye drops and withholding treatment for 4 weeks. In July 2017, he elected to discontinue therapy. His leg lesions completely resolved off of vemurafenib and cobimetinib, and as of November 2017 CT scans, he continues to have no evidence of disease.

## Discussion

Vemurafenib-induced granulomatous dermatitis, vasculitis, panniculitis and erythema nodosum-like lesions occur in <2% of patients,<sup>17,18</sup> and only four case reports have documented erythema nodosum-like side-effects during combination BRAF and MEK inhibition.<sup>19</sup> To the best of our knowledge, this is the first case of cobimetinib- and vemurafenib-induced granulomatous dermatitis and erythema induratum reported in the literature. While related to erythema nodosum, erythema induratum displays a different histopathologic subcutaneous fat reaction pattern that is typically caused by *Mycobacterium tuberculosis* antigenic stimulus or other underlying disorders.<sup>20</sup> In the literature, erythema induratum is typically referred to as ‘erythema-nodosum-like lesions’.

Our patient developed granulomatous dermatitis and then erythema induratum after approximately 13 and 26 months of combination BRAF and MEK inhibition, respectively. Similar to the literature documenting erythema nodosum-like lesions, our patient’s erythema induratum occurred on his lower extremities, although his diagnosis exceeded the wide range of 7 days to 16 months from treatment initiation to lesion onset.<sup>19</sup> Our patient also had a stuttering course of lesion flares that would spontaneously resolve or recur regardless of dose-reduction. This is in keeping with the apparent lack of ability to predict resolution of erythema nodosum-like lesions from change in BRAF inhibitor management: while approximate 60% of patients had resolution of their lesions without reduction or interruption of their BRAF inhibitor, 30% had persistent or recurrent lesions despite change to BRAF inhibitor dosing.<sup>19</sup>

The mechanism of BRAF inhibitor-induced granulomatosis and panniculitis has yet to be elucidated, although the pathogenesis of panniculitis is thought to be an antigen-induced deposition of immune complexes in the venules of subcutaneous fat septae.<sup>21</sup> Neutrophil migration is partially regulated by the MAPK pathway.<sup>22</sup> Hence, deregulation of the MAPK pathway may lead to abnormal trafficking of neutrophils and create neutrophilic panniculitis,<sup>19</sup> although neutrophilic lobular panniculitis has been

known to occur in the setting of non-cytotoxic anti-neoplastic medications.<sup>23</sup>

Management for BRAF inhibitor-associated erythema nodosum-like lesions ranges from withholding the offending drug, non-steroidal anti-inflammatories, or topical or systemic glucocorticoids; unfortunately, treatment failure can occur in 28%–37% of cases.<sup>19</sup> Our patient’s granulomatous dermatitis fully resolved with cessation of both drugs. His subsequent erythema induratum would recur and spontaneously resolve while on treatment, with complete resolution upon discontinuing BRAF and MEK inhibition. Furthermore, he also has complete radiographic response from vemurafenib and cobimetinib. It is unknown whether melanoma response is associated with BRAF and MEK inhibition-induced granulomatosis or erythema induratum. Currently, there is no trend in the literature to suggest either a better or worse response in those who develop erythema nodosum-like lesions.<sup>19</sup>

In conclusion, we demonstrate erythema induratum in a patient treated with vemurafenib plus cobimetinib. BRAF inhibitor-induced inflammatory skin reactions are rare events of uncertain prognostic potential. Regular dermatologic assessment should be performed on patients taking BRAF inhibitors for detection and management of these toxicities.

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## Informed consent

Informed consent has been obtained from the patient in this case report for textual description, photograph and histopathology pictures.

## References

1. Dossett LA, Kudchadkar RR and Zager JS. BRAF and MEK inhibition in melanoma. *Expert Opin Drug Saf* 2015; 14(4): 559–570.
2. Wellbrock C and Hurlstone A. BRAF as therapeutic target in melanoma. *Biochem Pharmacol* 2010; 80(5): 561–567.
3. Smalley KS and Sondak VK. Melanoma – an unlikely poster child for personalized cancer therapy. *N Engl J Med* 2010; 363(9): 876–878.
4. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011; 29(10): 1239–1246.
5. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364(26): 2507–2516.

6. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; 17(9): 1248–1260.
7. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol* 2017; 28(7): 1631–1639.
8. Sinha R, Edmonds K, Newton-Bishop JA, et al. Cutaneous adverse events associated with vemurafenib in patients with metastatic melanoma: practical advice on diagnosis, prevention and management of the main treatment-related skin toxicities. *Br J Dermatol* 2012; 167(5): 987–994.
9. Wantz M, Spanoudi-Kitrimi I, Lasek A, et al. Vemurafenib-induced toxic epidermal necrolysis. *Ann Dermatol Venereol* 2014; 141(3): 215–218.
10. Hersey P. Community experience of vemurafenib for BRAF(V600) melanoma. *Lancet Oncol* 2014; 15(4): 369–370.
11. Larkin J, DelVecchio M, Ascierto PA, et al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. *Lancet Oncol* 2014; 15(4): 436–444.
12. Huang V, Hepper D, Anadkat M, et al. Cutaneous toxic effects associated with vemurafenib and inhibition of the BRAF pathway. *Arch Dermatol* 2012; 148(5): 628–633.
13. Chu EY, Wanat KA, Miller CJ, et al. Diverse cutaneous side effects associated with BRAF inhibitor therapy: a clinicopathologic study. *J Am Acad Dermatol* 2012; 67(6): 1265–1272.
14. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med* 2012; 367(2): 107–114.
15. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012; 367(18): 1694–1703.
16. Sanlorenzo M, Choudhry A, Vujic I, et al. Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. *J Am Acad Dermatol* 2014; 71(6): 1102.e1–1109.e1.
17. Lacouture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist* 2013; 18(3): 314–322.
18. Sinha R, Larkin J, Gore M, et al. Cutaneous toxicities associated with vemurafenib therapy in 107 patients with BRAF V600E mutation-positive metastatic melanoma, including recognition and management of rare presentations. *Br J Dermatol* 2015; 173(4): 1024–1031.
19. Mossner R, Zimmer L, Berking C, et al. Erythema nodosum-like lesions during BRAF inhibitor therapy: report on 16 new cases and review of the literature. *J Eur Acad Dermatol Venereol* 2015; 29(9): 1797–1806.
20. Gilchrist H and Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther* 2010; 23(4): 320–327.
21. Blake T, Manahan M and Rodins K. Erythema nodosum – a review of an uncommon panniculitis. *Dermatol Online J* 2014; 20(4): 22376.
22. Liu X, Ma B, Malik AB, et al. Bidirectional regulation of neutrophil migration by mitogen-activated protein kinases. *Nat Immunol* 2012; 13(5): 457–464.
23. Ramdial PK and Naidoo DK. Drug-induced cutaneous pathology. *J Clin Pathol* 2009; 62(6): 493–504.