DOI: 10.7860/JCDR/2026/82377.22441

Case Report

Dermatology Section

Effective Use of Low-dose Isotretinoin for Trametinib-induced Acneiform Eruptions in Metastatic Melanoma: A Case Report

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ABSTRACT

Trametinib, a Mitogen-activated Protein Kinase (MEK) inhibitor used in the treatment of B-Raf proto-oncogene (BRAF) mutated metastatic melanoma, frequently causes acneiform eruptions that may impair patient compliance. We report a case of a 25-year-old male with metastatic melanoma harbouring BRAF fusion mutations who developed severe papulopustular eruptions four weeks after initiating trametinib therapy. Conventional therapy with oral doxycycline and topical antimicrobials resulted in only transient improvement, with rapid recurrence. Low-dose oral isotretinoin (0.4 mg/kg/day) was started in view of refractory disease, leading to marked improvement within four weeks and near-complete clearance by eight weeks, without requiring trametinib interruption. The patient tolerated isotretinoin well, with no adverse effects or laboratory abnormalities, and remained free of recurrence after discontinuation. This case highlights the effectiveness and safety of low-dose isotretinoin in managing MEK inhibitor-induced cutaneous toxicity, allowing uninterrupted cancer therapy and improved patient comfort.

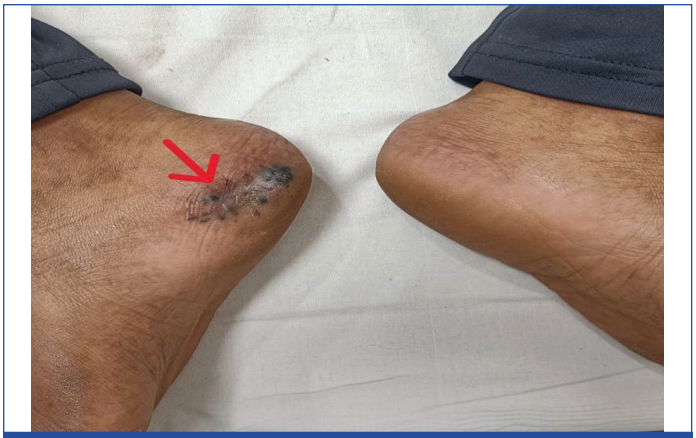
Keywords: Adverse effects, Antineoplastic agents, Mitogen-activated protein kinase inhibitor, Papulopustular rash, Retinoids, BRAF fusion

CASE REPORT

A 25-year-old man presented with a six-month history of a progressively enlarging pigmented lesion over the right heel, which was asymptomatic

The patient first noticed a small pigmented spot over the right heel that gradually increased in size over six months without pain, pruritus, bleeding or ulceration. He had no history of any other dermatological or systemic comorbidities. He had not received prior chemotherapy, radiotherapy or targeted therapy before starting trametinib.

[Table/Fig-1] shows a clinical photograph with a hyperpigmented lesion over the lateral aspect of the right heel.



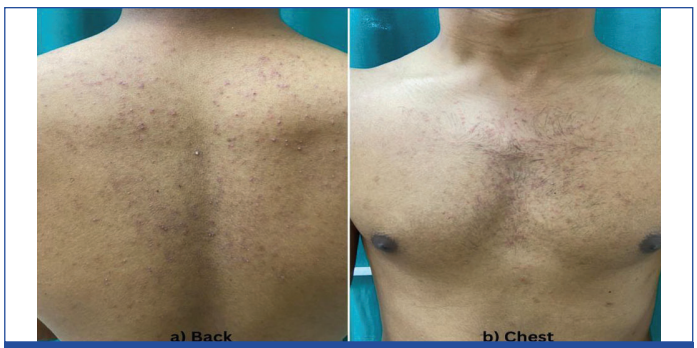
[Table/Fig-1]: Clinical photograph showing a hyperpigmented, irregularly surfaced plaque over the lateral aspect of the right heel, consistent with post-excision changes in a case of malignant melanoma. The contralateral heel is normal for comparison.

Biopsy revealed epidermis with pagetoid upward scatter of atypical melanocytes, dermis with nests and sheets of pleomorphic melanocytes and atypical mitosis confirmed malignant melanoma. Immunohistochemistry revealed positivity for HMB-45, S100, and SOX10, supporting the diagnosis malignant melanoma. Positron-Emission Tomography-Computed Tomography (PET-CT) scan demonstrated hypermetabolic activity in the right inguinofemoral and iliac lymph nodes, consistent with regional metastasis.

Molecular profiling revealed a BRAF-AGAP3 fusion, known to constitutively activate the MAPK pathway [1]. In addition, a MAD1L1-BRAF fusion has been described in melanocytic tumours, although functional and clinical data remain limited, particularly outside Spitz melanoma [2]. Based on this, the patient was started on oral trametinib monotherapy at 2 mg/day, considering the sensitivity of the BRAF fusion to MEK inhibition.

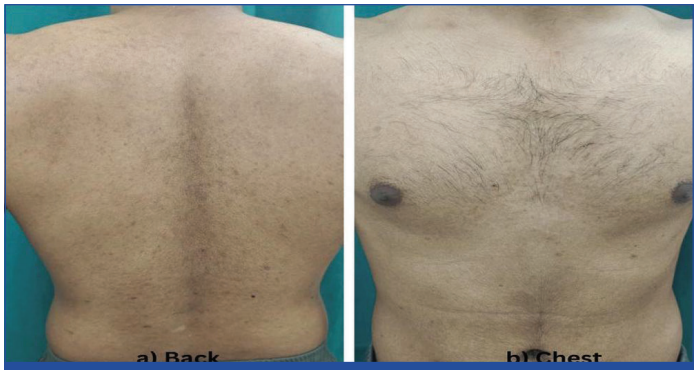
Four weeks into therapy, the patient developed widespread asymptomatic erythematous papules and pustules on the face, chest, and back, clinically consistent with an acneiform eruption [Table/Fig-2a,b]. These lesions were monomorphic, inflammatory, and non-comedonal, without any systemic symptoms. The patient was diagnosed with trametinib-induced acneiform eruptions.

Initially the patient was treated with topical clindamycin 1% gel and oral doxycycline 100 mg once a day. Although a transient improvement was noted after two months, the lesions quickly recurred with equal or greater severity. This led to considerable distress to the patient and raised concerns about the long-term continuation of trametinib.



[Table/Fig-2]: Clinical photograph showing papulopustular acneiform lesions at onset (week 0) on the: a) back; and b) chest.

Given the refractory nature of the eruption, low-dose oral isotretinoin was initiated at 20 mg/day (approximately 0.4 mg/kg/day). Within four weeks, marked improvements in both the inflammatory and pustular components were observed. At the 8-week follow-up, the skin was almost entirely clear of lesions [Table/Fig-3a,b].



[Table/Fig-3]: Near-complete clearance of lesions at week eight after initiating isotretinoin on the a) back, and b) chest.

The isotretinoin dose was then tapered to 10 mg/day and continued for another eight weeks as maintenance. Subsequently, isotretinoin was discontinued and the patient was maintained on topical clindamycin 1% and tretinoin 0.05%.

The patient tolerated isotretinoin well, with no reported adverse effects, such as xerosis, cheilitis, or laboratory abnormalities. Serial monitoring of liver function tests and lipid profiles remained within normal limits. Importantly, the patient remained on trametinib throughout this period without interruption or dose reduction. Follow-up PET-CT after three months of treatment revealed a reduction in size and metabolic activity of metastatic lymph nodes, confirming continued oncologic response. Furthermore, there was no recurrence of acneiform eruptions three months after discontinuation of isotretinoin.

DISCUSSION

Melanoma is an aggressive cutaneous malignancy with a high propensity for metastasis, contributing to most skin cancer-related deaths globally [3,4]. Advancements in molecular diagnostics and targeted therapy have revolutionised its treatment, particularly in cases harboring mutations in the BRAF gene [5]. Approximately 40-60% of melanomas exhibit BRAF mutations, most commonly the V600E mutation, which leads to constitutive activation of the MAPK/ERK signalling pathway [3]. Targeted inhibition of this pathway using BRAF inhibitors (e.g., dabrafenib, vemurafenib) and MEK inhibitors (e.g., trametinib, cobimetinib) has significantly improved survival in patients with advanced melanoma [3-5].

Trametinib is an oral, selective MEK1/2 inhibitor approved for use either alone or in combination with BRAF inhibitors [3]. Acneiform eruptions are among the most frequently reported cutaneous adverse events associated with MEK inhibitors, including trametinib, with an incidence ranging from 20% to 77%, depending on the dosage, combination with BRAF inhibitors, and patient-specific factors [4,6]. The mechanism is believed to be related to MAPK pathway disruption within keratinocytes and sebocytes, leading to follicular hyperkeratinisation, inflammation, and altered differentiation [7]. Unlike typical acne vulgaris, these eruptions are monomorphic, predominantly inflammatory, and lack comedones.

While most cases respond to topical therapy and tetracycline group of antibiotics, a subset may be refractory [7]. In the present case, the partial response to doxycycline and rapid recurrence suggested the need for alternative systemic therapy. Isotretinoin, owing to its ability to reduce sebaceous gland activity, normalises follicular keratinisation and inhibits neutrophil chemotaxis, making it a logical therapeutic option in such scenarios [8].

Caruana M et al., reported similar findings where isotretinoin led to the resolution of trametinib-induced acneiform eruptions without discontinuation of cancer therapy [9]. The present case further supports this, demonstrating complete lesion clearance with a well-tolerated low dose of isotretinoin. Importantly, this intervention allowed uninterrupted administration of the MEK inhibitor, which is critical in advanced melanoma, where delays or dose reductions can influence survival outcomes.

The absence of adverse effects in our patient underscores the safety of low-dose isotretinoin when appropriately monitored. This case highlights the importance of early dermatological intervention and close collaboration between oncology and dermatology teams in managing targeted therapy-related cutaneous toxicities.

CONCLUSION(S)

Low-dose isotretinoin proved effective and well-tolerated in managing refractory trametinib-induced acneiform eruptions. Its use enabled uninterrupted targeted cancer therapy without recurrence. Early dermatologic intervention is essential to maintain treatment adherence and optimise patient outcomes.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 20, 2025
- Manual Googling: Nov 20, 2025
- iThenticate Software: Nov 24, 2025 (5%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 02, 2025**
Date of Peer Review: **Nov 08, 2025**
Date of Acceptance: **Nov 26, 2025**
Date of Publishing: **Feb 01, 2026**