MEK Inhibitor–Induced Dusky Erythema
Characteristic Drug Hypersensitivity Manifestation in 3 Patients

Urvi Patel, MD; Lynn Cornelius, MD; Milan J. Anadkat, MD

IMPORTANCE MEK inhibitors are being evaluated in clinical trials for treatment of different malignant neoplasms; trametinib dimethyl sulfoxide was approved by the US Food and Drug Administration for melanoma in 2013. We present 3 cases of patients receiving MEK inhibitors who developed an atypical eruption.

OBSERVATIONS Three patients who were receiving different MEK inhibitors (selumetinib, cobimetinib, and trametinib) developed an eruption, all associated with unique duskiness. Drug hypersensitivity was confirmed by histopathologic testing in 2 of the 3 cases. The skin eruption responded well to corticosteroids and did not recur when treatment with the MEK inhibitor was restarted in 2 of the patients.

CONCLUSIONS AND RELEVANCE The typical skin reaction associated with MEK inhibitors is a papulopustular eruption. To our knowledge, the dusky erythema that occurred in the 3 patients described here has not previously been reported for this drug class.

REPORT OF CASES

Case 1
A man in his 60s with stage 4 pancreatic cancer was receiving MK2206, 135 mg/wk, as part of a clinical trial. Twelve days after the start of therapy, he presented with a generalized eruption and mild pruritus. He had diffuse targetoid patches with central duskiness (Figure 1). The eruption was grade 2 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Table). Study medications were withheld because of the eruption. The eruption had started to fade with topical corticosteroid treatment before the drugs were discontinued; however, the therapy was not restarted owing to an elevated alkaline phosphatase level and fatigue. The eruption had resolved by the time of the patient's follow-up visit 4 weeks after discontinuation of the study drugs.

Case 2
A woman in her 40s was receiving vemurafenib, 960 mg, twice daily on days 1 to 28 and study drug GDC-0973 (cobimetinib), 60 mg/d, on days 1 to 21 for metastatic melanoma that was BRAF V600E mutated. She developed a diffuse eruption on day 28 of treatment. Findings from the physical examination revealed coalescing urticarial patches with surrounding duskiness that was grade 2 according to the CTCAE, version 4.0 (Figure 2A). Histopathologic examination showed a superficial perivascular lymphocytic infiltrate with rare eosinophils (Figure 2B and C). Both medications were stopped for 7 days by the oncologist owing to the eruption, and a slow tapering regimen of oral prednisone, starting at 60 mg/d, was instituted. Cobimetinib therapy was re instituted at 40 mg/d, and the patient continued to receive oral prednisone, 10 mg/d, throughout treatment because of arthralgias associated with...
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Discussion

Targeted therapies have become a part of treatment for many malignant neoplasms, including metastatic melanoma. The mitogen-activated protein kinase (MAPK) pathway, also known as the RAS/RAF/MEK/ERK pathway, has become a new target for cancer therapy owing to its downstream position in the signaling cascade. The MAPK pathway influences multiple cellular functions, including cell survival, proliferation, differentiation, and apoptosis. Mutations in the MAPK pathway can be driver mutations in cancer development and play a role in the development of drug resistance. Such mutations have been noted in several cancers, including melanomas. Multiple agents that inhibit MEK and other kinases in this pathway are currently in clinical trials as adjuvant treatment for several malignant neoplasms, including pancreatic cancer and metastatic melanoma.

A cutaneous eruption is one of the most commonly reported adverse effects for the MEK inhibitor class of targeted therapies. The incidence of skin eruption ranged from 57% to 93% in phase 1, 2, and 3 clinical studies and was typically of grade 1 or 2 severity. The incidence of grade 3 or greater skin toxic effects secondary to MEK inhibitors was reported to be less than 10%. Skin eruption has been recognized as a dose-limiting toxic effect of MEK inhibitors, but in most cases it did not require drug cessation. Commonly reported dermatologic adverse effects of MEK inhibitors are similar to those of epidermal growth factor receptor inhibitors, although with a lower level of severity. The most common dermatologic adverse effect reported with MEK inhibitors is a papulopustular eruption, with an incidence of 40% to 93%. Other adverse effects have included paronychia and fissuring, hair changes, xerosis, mucositis, and pruritus. Other types of eruptions include a maculopapular eruption and erythema. We report unusual drug hypersensitivity, with lesions ranging from urticarial to targetoid but all with a distinctive central duskiness. Although this eruption is reminiscent of erythema multiforme, the lack of interface changes and dyskeratosis on histopathologic examination clearly distinguishes between the 2 diagnoses.

Recognition of this unique clinical phenotype is significant for helping the physician determine the culprit drug because many patients with cancer may be receiving multiple medications. Other than pruritus, the eruption was asymptomatic in our series of patients. No mucosal involvement or other systemic symptoms were noted. In distinction to the use of BRAF inhibitors (in particular, vemurafenib) as a solo agent, an increased incidence of squamous cell carcinomas has not been noted with MEK inhibitors used alone or in combination with other agents. As shown in our patients, successful treatment of this MEK inhibitor–associated cutaneous eruption can include a drug holiday and oral corticosteroid therapy, with reinstitution of the drug at a lower dose without recurrence.

Table. Maculopapular Rash Grading According to CTCAE, Version 4.0

<table>
<thead>
<tr>
<th>Grade</th>
<th>Maculopapular Eruption</th>
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<tbody>
<tr>
<td>1</td>
<td>Macules/papules covering &lt;10% BSA with or without symptoms (eg, pruritus, burning, tightness)</td>
</tr>
<tr>
<td>2</td>
<td>Macules/papules covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL</td>
</tr>
<tr>
<td>3</td>
<td>Macules/papules covering &gt;30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting self-care ADL</td>
</tr>
<tr>
<td>4</td>
<td>No definition</td>
</tr>
<tr>
<td>5</td>
<td>No definition</td>
</tr>
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</table>

Abbreviations: ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events.

* Adapted from the Cancer Therapy Evaluation Program.
Conclusions

The MEK inhibitors are a newer class of targeted therapies, and one of these, trametinib, was recently approved by the US Food and Drug Administration for treatment of metastatic melanoma. Cutaneous toxic effects have been reported as one of the most common adverse drug events. We present a drug hypersensitivity eruption to MEK inhibitors that is distinctive because of the characteristic dusky appearance. It responds well to temporary drug cessation and oral prednisone therapy.

REFERENCES

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Case Report/Case Series  Research


NOTABLE NOTES

Medical Problems in the Trenches

Walter H. C. Burgdorf, MD; Leonard J. Hoenig, MD

Sometimes we can learn a lot even from a single word. Take, for example, the word “trench,” which means a ditch used for concealment and protection in war. One hundred years ago, that word took on a more horrifying meaning when it began to describe the most devastating form of war mankind had ever invented: the “trench warfare” of World War I.

For 4 years, Western Allies and Germans faced each other across an extensive series of trenches extending from the Franco-Swiss border to the Belgian coast. Separated by a no-man’s land of a few hundred meters, the armies fought ferociously for precious meters of land, enduring huge casualties.1

What was life like in the trenches? The unsanitary conditions resulted in epidemics of dysentery and the constant presence of parasites, such as scabies and lice, as well as fungal infections. There were no antibiotics, so every wound was potentially fatal through gangrene or other bacterial infections. The continuing exposure to danger in the confined trench spaces led to numerous psychological problems, such as shell shock. There were 3 diseases that became coupled with the name “trench”: “trench fever,” “trench foot,” and “trench mouth.”

Trench fever: The pervasive presence of lice facilitated the transmission of Rickettsia quintana, which is transferred in the lice feces and introduced into the host by scratching or trauma.2 After a 1 to 3 week incubation period, the patient presents with fever, chills, and tenderness, especially over the shins (shinbone fever is a synonym). A red macular truncal rash often occurs. There may be relapsing fevers, and the bacteremia persists for years. Today, antibiotics provide quick relief, but then only symptomatic care was available. Thus, the typical patient was unfit for duty for several months. Fortunately, the far more feared epidemic typhus caused by Rickettsia prowazekii and also transmitted by lice did not appear in the Western trenches.

Trench foot: Prolonged exposure to moisture and cold without freezing produces trench or immersion foot. There is profound neurovascular damage with pain, swelling, and ulcerations, predisposing the soldier to gangrene. Treatment consists of drying and gentle rewarming—which was not possible in the trenches. Even after healing, the injured feet remain exquisitely temperature-sensitive.

Trench mouth: Brushing one’s teeth had not yet become part of the universal daily routine and was ignored in the trenches. An acute synergistic oral infection involving normally harmless denizens of the oral cavity produced bad breath, ulcers, bleeding, and sloughing of tissue. It made eating and swallowing difficult. Today, it is known as acute necrotizing ulcerative gingivitis.

We conclude this remembrance of World War I with a poem called “Suicide in the Trenches.” The poet was Siegfried Sassoon (1886-1967), an officer in the British army decorated for bravery. His poem tells the story of a young, nameless soldier and his terrible ordeal on the Western Front.

Suicide in the Trenches

I knew a simple soldier boy
Who grinned at life in empty joy,
Slept soundly through the lonesome dark,
And whistled early with the lark.

In winter trenches, cowed and glum,
He put a bullet through his brain.
No one spoke of him again.

You smug-faced crowds with kindling eye
Who cheer when soldier lads march by,
Sneak home and pray you’ll never know
The hell where youth and laughter go.

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