A Case of Acute Generalized Exanthematous Pustulosis due to Trametinib
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Introduction
Trametinib, a MEK inhibitor, was approved by the FDA in 2013 as a single agent treatment for malignant melanoma1. Trametinib reversibly binds MEK proteins, preventing continued activation of the mitogen activated protein kinase pathway which leads to cell proliferation and survival1. Treatment with trametinib has been shown to provide an overall survival benefit over standard chemotherapy1. Common side effects from the medication include skin rash, diarrhea, peripheral edema, fatigue, acneiform eruptions, and nausea1. When trametinib is used as monotherapy, acneiform eruptions have been documented in approximately 75% patients1. Generally this can be managed with doxycycline and topical antibiotics or antiseptic washes but occasionally requires a decrease in dosing of the medication1. While cutaneous side effects are commonly seen with trametinib, there have been no reports of acute generalized exanthematous pustulosis in the literature to date.

Case Presentation
An 80-year-old male undergoing treatment for stage IV malignant melanoma presented to the clinic with a new onset, diffuse rash, which had been present for eight days. The rash appeared suddenly and spread over a few hours but had remained relatively stable since day one. Associated symptoms included mild soreness of the skin but there was no associated pruritus. He had no improvement with Benadryl taken at home. There was no evidence of eye or mucous membrane involvement. He was otherwise feeling well with a negative review of systems. Eleven days before the onset of the rash, the patient was started on trametinib, his only new medication, after failing treatment with pembrolizumab and ipilimumab for metastatic melanoma. He had no history of psoriasis but did have a history of adverse drug reactions.

Vital signs were notable for a fever of 38.7°C. Physical exam revealed multiple non-follicular exanthematous papules and pustules with scattered yellow-white crust overlying erythematous plaques on the scalp, face, ears, neck, and central upper chest and back. The bilateral arms and abdomen had scattered erythematous papules and pustules. Laboratory evaluation was significant for a white blood cell count of 11.68 K/μL. No evidence of hepatic or renal involvement was found and no pulmonary symptoms were present. A 4 mm punch biopsy was performed of a new, intact pustule on the chest. Pathology showed intracorneal neutrophils and upper dermal neutrophils with leukocytoclasis and eosinophils consistent with acute generalized exanthematous pustulosis (AGEP).

We initiated treatment with triamcinolone 0.1% cream and sodium sulfacetamide 10% lotion to affected areas. Trametinib had been discontinued by the primary team two days prior to presentation due to the extentiveness of the rash. At his follow-up visit 16 days later, the rash had resolved after postpustular desquamation of the affected skin. We established a definite diagnosis of AGEP based on the EuroSCAR criteria (8 points).

Discussion
AGEP is rare, potentially severe, skin rash that is most commonly seen as an adverse reaction to medications2,3. Characteristically, AGEP occurs after exposure to antibiotics and develops within 24-48 hours of drug exposure3,4. When AGEP is caused by nonantibiotic medications, there appears to be a delayed onset from time of exposure to presentation with a median of 11 days5. The exanthem is classically comprised of sterile, non-follicular, pinhead-sized pustules overlying erythematous skin5,6. Body folds are often affected first with generalization to the trunk and, to a lesser extent, the limbs within a few hours5. Macular membranes are affected in about 25% of cases but involvement is typically limited to one site, most commonly the lips or buccal mucosa5. Pruritus or a burning sensation may be present5.

Systemic features supporting a diagnosis of AGEP include fever ≥ 38°C and leukocytosis ≥ 7.0 K/μL, which are seen in 36% and 79% respectively5. Internal organ involvement is seen in approximately 20% of cases with hepatic, renal and pulmonary dysfunction most commonly reported5. Features consistent with AGEP on histology include papillary dermal edema with neutrophil or eosinophil infiltrate with intraconal, subconal, and/or intraepidermal pustules4.

The mainstay of treatment is cessation of the causative medication. Supplemental treatments are supportive and include systemic or topical corticosteroids, antiseptic solutions and/or antihistamines5. With treatment, most cases of AGEP will resolve within 7 - 15 days but often occurs with medication re-exposure6.

In addition to identifying trametinib as a potential cause of AGEP, our case merits additional discussion because of its uncommon presentation. The time frame from drug initiation to development of AGEP was delayed, as demonstrated in some other cases of non-antibiotic induced AGEP. Second, the distribution of the exanthem did not start in or favor the body folds as is typically seen in AGEP but rather corresponded with a typical sebaceous distribution more commonly seen with acneform eruptions. These unique features emphasize the potential difficulty distinguishing trametinib’s common acneform eruption and AGEP. It is important that the correct diagnosis is made given the difference in their clinical implications and managements as outlined above. Nevertheless our patient obtained a case score of 8 according to the validation score of the EuroScar study group, supporting the diagnosis of definite AGEP.

References