


CASE REPORT

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Cutaneous adverse reactions in B-RAF positive metastatic melanoma following sequential treatment with B-RAF/MEK inhibitors and immune checkpoint blockade or vice versa. A single-institutional case-series

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Abstract

Background: With the advent of immune-checkpoint inhibitors and targeted treatments (TT), there have been unprecedented response rates and survival in advanced melanoma, but the optimal sequencing of these two treatments modalities is unknown. Combining or sequencing these agents could potentially result in unique toxicities. Cutaneous adverse events (CAE) after sequential exposure to these agents represents one toxicity that needs further description.

Methods: After retrospectively reviewing charts of patients from 2015 to 2018, we identified six patients who experienced CAEs after recent exposure to sequential immunotherapy and TT or vice versa for the treatment for metastatic melanoma at the University of North Carolina, Chapel Hill. Skin biopsies were available in five patients.

Results: Five patients received TT after immunotherapy, and one patient received immunotherapy after TT. TT consisted of vemurafenib/cobimetinib (V/C) in five patients with four patients starting V/C immediately before manifesting with a CAE. In patients receiving V/C after immunotherapy, the median time from beginning V/C to development of CAE was 14.5 days. The clinical presentation of diffuse morbilliform rash, fevers, hypotension, and end-organ damage raised concern for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. Histopathological features of lympho-eosinophilic infiltrate were supportive of a drug eruption. Immunotherapy or TT were re-initiated in five patients within 1–8 weeks after resolution of the index CAE. This resulted in two patients re-experiencing the CAE. Both of these patients were off prednisone at the time of therapy re-initiation, whereas none of the patients who were restarted on targeted therapy with a steroid overlap had a rash recurrence.

Conclusions: Sequential treatment using immunotherapy and TT, especially the sequence of V/C after immunotherapy appears to be the most common trigger for CAE with a median time to onset of approximately 2 weeks. Although the clinical presentation of these CAEs can be dramatic, they respond well to prednisone therapy. This unique presentation suggests that it may be reasonably safe to re-challenge certain patients with a steroid overlap after rash resolution.

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Keywords: Cutaneous adverse events, Metastatic melanoma, B-RAF inhibitors, Immune checkpoint blockade, Vemurafenib/cobimetinib, DRESS syndrome

Introduction

With the advent of immune-checkpoint inhibitors and novel targeted therapies (TT), the treatment landscape for melanoma has witnessed a paradigm shift with unprecedented survival and response rates both in the adjuvant and the metastatic settings [1]. This, in turn, has prompted a revolution that has gradually spread across certain other tumor types, resulting in remarkably improved outcomes. Around 40–50% of cutaneous melanomas harbor mutations in the B-RAF gene with V600E accounting for 80–90% in this category. One of the standard approaches for B-RAF V600E mutated melanomas involves using B-RAF inhibitors in conjunction with MEK inhibitors [2]. Immune-checkpoint blockade (ICB) involving the use of monoclonal antibodies to modulate the immune checkpoints such as programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) is the other rapidly evolving approach that has demonstrated strong potency and durable efficacy in the frontline treatment of advanced melanomas including B-RAF mutated melanomas [1, 3].

In addition to various clinical factors, determining the primary and the salvage agent of choice to treat advanced-stage B-RAF V600E melanomas can be guided by the differential activities of ICB and TT. For example, TT have a rapid onset of action while ICB produces sustained responses providing an overall survival “tail” [1, 4]. Also, in response to disease progression, sequencing ICB and TT in B-RAF mutated melanoma is a reasonable approach frequently practiced in the real-life setting. The clinical benefit of a sequencing approach is supported by compelling pre-clinical data demonstrating the immune modulatory effects of TT that may serve to augment an endogenous anti-tumor response and thus achieve synergy with ICB [5, 6]. Presently, however, the paucity in efficacy and toxicity data from randomized studies tends to be a barrier in implementing these sequential or combination strategies into regular clinical practice.

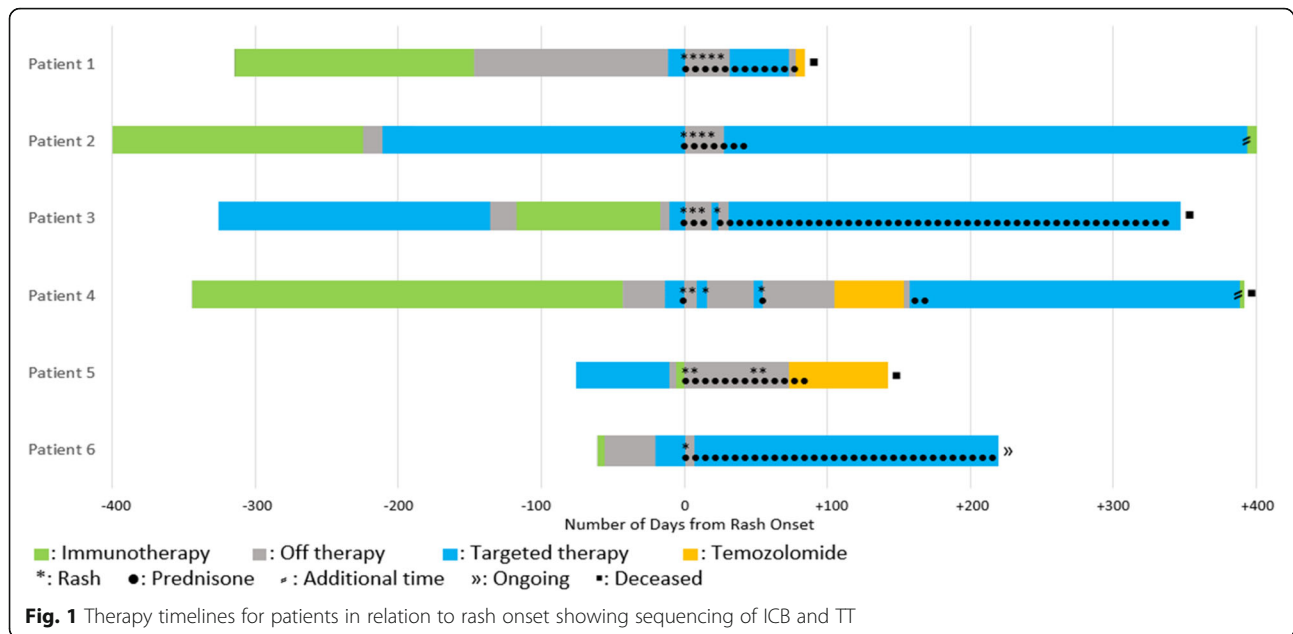
In our case series, we focus on patients treated with ICB followed by TT, or vice versa, who experienced cutaneous toxicities with unique histological patterns, a feature that has not been well described in the literature. We also attempt to understand certain common denominators that could have contributed to these presentations. Furthermore, we explore possible mechanisms of toxicity and diagnostic pitfalls that could help guide management in such scenarios.

Materials and methods

After institutional review board approval, we retrospectively reviewed charts from March 2015 to September 2018 to identify patients experiencing cutaneous adverse events (CAE) on receiving sequential ICB and TT or vice versa for the treatment of metastatic melanoma at the University of North Carolina, Chapel Hill. We identified five patients who received TT after ICB and one patient who received ICB after TT. Skin biopsies were available in five patients for better characterization of the cutaneous reactions. We also collected relevant data on laboratory parameters, clinical course, and management.

Results

(Table 1) All our patients were of Caucasian ethnicity with a median age of 58 years when diagnosed with CAE. Five of the six patients were female. The sequence of treatment timeline and CAE are depicted in Fig. 1. A total of five cases (patients 1–4 and patient 6) received ICB before TT as the two most recent treatment modalities before experience a CAE. Only Patient 5 received ICB after TT. In the five patients who received ICB before TT, the median time from discontinuation of the most recent ICB to CAE was 56 days (24–228 days). In four patients (patients 1–4) nivolumab was given for ICB before TT. Pembrolizumab was utilized for ICB in two patients, with patient-5 receiving it after TT and patient-6 receiving it before TT. ICB was primarily used as a single agent with the only exception being patient-1 where one dose of ipilimumab had been given with nivolumab followed by nivolumab alone. Before switching to TT, the median number of ICB doses for the five patients receiving TT after ICB was 12 (1–22 doses). In our cohort, TT consisted of vemurafenib/cobimetinib (V/C) in five patients (patients-1 and 3–6) with four patients (patients 1, 3, 4 and 6) receiving V/C immediately before manifesting with a CAE. In patients that specifically received TT in the form of V/C after ICB, the median time from starting V/C to development of CAE was 14.5 days (12–21 days). Patient 2 was on dabrafenib/trametinib (D/T) for a considerable period (214 days) before developing the CAE. The timeline for the rash in patient-2 coincided with starting amoxicillin/clavulanic acid for a pneumonia. Patient-5 developed the CAE immediately after one dose of pembrolizumab. Patient-3 had been previously treated



with D/T before switching to ICB but tolerated both these agents for a considerable time without any toxicity. However, when switched from ICB to V/C, he manifested with the rash immediately within 16 days from the switch. All four patients who presented with signs and symptoms consistent with systemic inflammatory response syndrome (SIRS) including high-grade fevers, hypotension, and end-organ damage required hospitalization (patients 1, 2, 3 and 5). The values for C-reactive protein were available in three patients with all values measuring >150 mg/L (reference range <10.0 mg/L). Oral mucositis was an accompanying feature in two of the six patients (patients 1 and 2). Most of the patients had grade-4 CAE based on the Common Terminology Criteria for Adverse Events (CTCAE 4.03) system (Table 1). The CAE was mainly characterized by a diffuse erythematous morbilliform eruption involving $\geq 30\%$ body surface area (Fig. 2) with histopathology primarily comprising of a lympho-eosinophilic infiltrate (Fig. 3b). Patient 2 was the only exception where sub-epidermal vesicle formation suggestive of bullous pemphigoid was seen. As part of a comprehensive assessment, patient-1 had serum cytokines measured, and notably, the level for the interleukin-2 receptor (IL-2R) was seen to be >20 times the upper limit (Table 1).

(Table 2) Apart from supportive care, corticosteroids were an integral part of the management of the CAE. The dose and duration for steroid use were based on the severity of the initial presentation. Patients that had more severe clinical presentations were started on higher doses with a protracted taper (patient-2, 3 and 5) while

as patients that had relatively milder clinical presentations and lower intensity rash (for example patient-4 and 6) were started on lower doses which were continued for a shorter period of time. After stopping the treatment and initiating supportive care, by week three resolution in the CAE was observed in a majority (patients 3–6), while patients-1 and 2 took approximately 6 weeks for the rash to resolve. ICB or TT was reinitiated in five patients within 1–8 weeks after resolution of the index CAE. This resulted in two patients (Patients 3 and 4) re-experiencing the CAE. Both of these patients were off prednisone at the time of therapy re-initiation, whereas none of the patients in our series who were restarted on TT with a steroid overlap (Patients 1, 2 and 6) had a rash recurrence. Patient 5 relapsed with a rash on day 54 after the index rash when she was tapered down to 5 mg prednisone. Following this, her dose for prednisone was increased again with a protracted taper. Patient 2 experienced controlled disease for more than 1 year after reinitiating TT without recurrence of adverse events. Patient 6 remains on TT, now greater than 6 months since reinitiating it. Despite the initial recurrence of rash in patient 3, he was able to be restarted on TT a second time, with steroid overlap, and to stay on this for greater than 9 months after that without additional CAEs. Patient 4 was switched to dabrafenib/trametinib (D/T) 166 days after the index CAE with gradual dose escalation, which she tolerated well despite rash recurrence when previously re-challenged with V/C. Subsequently, patient 4 had to be switched from D/T to ipilimumab due to disease progression and died within 1 month thereafter. Two of the six patients (patients 1 and 5) were noted to have disease progression on reevaluation after 4–8 weeks

Table 1 Therapy and Rash Characteristics

| Patient | Demographics at Time of Rash Onset | Therapy Sequence [(Days to Rash Onset (RO))] | Clinical Course | Lab Abnormalities | CTCAE Rash Grade (G), Characterization Location Initial Diagnosis | Histopathology | Confounding Variables | Current Survival Status |
|---------|------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------|
| 1 | 54 year old Caucasian female | I/N x1 -> N (Day -315 to -148) V/C (Day -12 to RO) | Hospitalized High grade fever Hypotension Oral mucositis | Hyponatremia Hypokalemia Elevated lactate (2.5XULN) Lymphocytopenia Elevated sIL-2R (20 X ULN) CRP 163 | G-4, Diffuse morbilliform eruption of trunk and extremities DRESS vs SJS vs drug reaction | Papillary dermal edema, slight basal layer vacuolization, superficial dermal perivascular lymphocytic infiltration and eosinophils | Started allopurinol 14 days prior to rash onset | Deceased |
| 2 | 60 year old Caucasian female | N (Day -408 to -228) D/T (Day -214 to RO) | ICU High grade fever Hypotension AMS Lip swelling Difficulty swallowing | Transaminitis | G-4, Diffuse morbilliform eruption of trunk and extremities Drug reaction vs sepsis vs DRESS | Subepidermal vesicle formation with eosinophils; positive direct immunofluorescence with linear IgG and IgA at the basement membrane zone suggestive of bullous pemphigoid or linear IgA bullous dermatosis | On course of amoxicillin-clavulanic acid at rash onset | Alive |
| 3 | 54 year old Caucasian male | D/T (Day -331 to -143) N (Day -122 to -24) V/C (Day -16 to RO) | Hospitalized High grade fever | Hyponatremia Elevated creatinine Lymphocytopenia | G-4, Diffuse targetoid lesions involving trunk, extremities and face SJS vs drug eruption (including DRESS) vs viral exanthem | Papillary dermal edema, slight basal layer vacuolization, superficial dermal perivascular lymphocytic infiltration and eosinophils | Symptoms of upper respiratory tract infection present immediately prior to rash onset | Deceased |
| 4 | 58 year old Caucasian female | N (Day -344 to -43) V/C (Day -13 to RO) | Outpatient management | None | G-4 Diffuse morbilliform eruption of trunk and extremities Drug reaction | No biopsy performed | Started with full doses of V/C when had been instructed to start at a reduced dose of each | Deceased |
| 5 | 59 year old Caucasian female | V/C (Day -75 to -11) P (Day -6 to RO) | ICU High grade fever Hypotension Tachycardia | Elevated creatinine Transaminitis Hyperbilirubinemia CRP 200 | G-4 Diffuse morbilliform eruption of trunk and extremities Sepsis vs DRESS vs pembrolizumab induced reaction | Papillary dermal edema, slight basal layer vacuolization, superficial dermal perivascular lymphocytic infiltration and eosinophils; few plasma cells, neutrophils, and a rare focus of parakeratosis | Concern for sepsis from cellulitis (re-fevered after antibiotics narrowed) | Deceased |
| 6 | 58 year old Caucasian female | P (Day -56) V/C (Day -21 to RO) | Outpatient management | Transaminitis Lymphocytopenia CRP 159 | G-2 Discrete scattered erythematous edematous plaques on extremities Drug reaction vs Sweets Syndrome vs early SJS | Papillary dermal edema, slight basal layer vacuolization, superficial dermal perivascular lymphocytic infiltration and eosinophils | No apparent confounding variables | Alive |

All days are calculated from rash occurrence (RO) being day 0, I Ipilimumab, N Nivolumab, P Pembrolizumab, V Vemurafenib, C Cobimetinib, D Dabrafenib, T Trametinib, sIL-2R Soluble interleukin-2 receptor, ULN Upper limit of normal, High grade fever = > 102, AMS Altered mental status, CRP C-reactive protein (reference range < 10.0 mg/L), SJS Stevens Johnson syndrome, DRESS Drug Reaction with Eosinophilia and Systemic Symptoms, CTCAE Common Terminology Criteria for Adverse Events (CTCAE 4.03)

of the CAE. In the entire cohort of 6 patients, two patients continue to be alive, receiving ongoing treatment (patient 6 on D/T and patient 2 on ICB).

Discussion

The biological rationale of combining or sequencing ICB with TT in metastatic melanoma stems from a growing

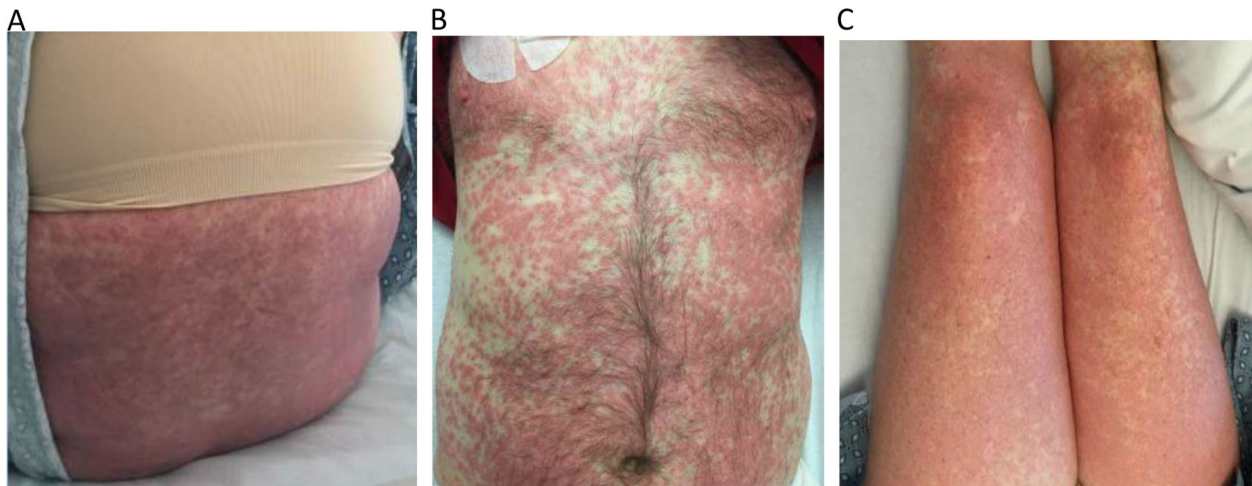


Fig. 2 Diffuse morbilliform eruption involving trunk (a, b) and extremities (c)

body of evidence supporting the favorable immune effects created by the oncogene-targeted therapies directed at the BRAF/MAPK pathway [4]. These beneficial effects that lead to potentiation of the immune effector function within the tumor microenvironment are mediated through various mechanisms, including effects on dendritic cell function, natural-killer-cell activation, increased HLA expression, upregulated expression of melanoma-derived antigens and T-cell homing to the tumor [5–7].

In this case series, we discuss cutaneous toxicity patterns in patients with B-RAF positive metastatic melanoma treated with sequential strategies involving ICB and TT in response to disease progression. Although very recently similar findings have been described by others in patients receiving TT after ICB [8], we provide a broader description of the unique histopathological characteristics and also attempt to address questions relating to

management strategies as well as the feasibility of re-challenging patients with these agents in certain circumstances.

As shown in Table 1, five of the six patients received ICB before TT and tolerated anti-PD-1 therapy without any overt concerns of toxicity. This raises speculation of immune priming by ICB followed by immune boosting by the TT which may result in aberrant immunomodulation. Findings from a recently published report elucidate worse clinical presentations associated with cutaneous toxicities to vemurafenib in patients previously exposed to nivolumab [9], lending proof of concept to the hypothesis of durable activation of T-effector cells by prior anti-PD-1 therapy triggering hypersensitivity to TT. Interestingly, in our series where patients had prior ICB use, the occurrence the CAE usually manifested within the first two to 3 weeks from

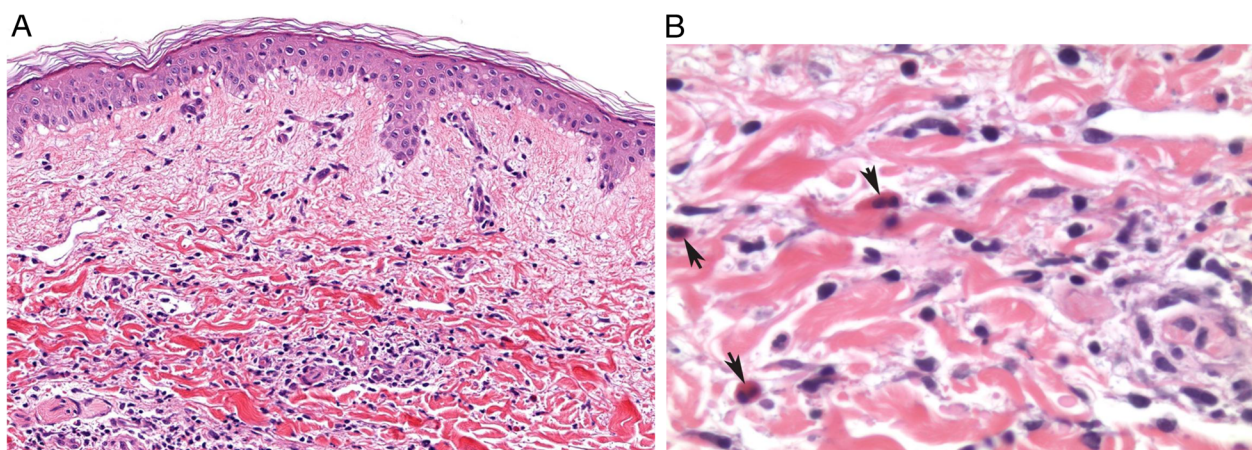


Fig. 3 Skin biopsy of rash with histology. **a** Skin biopsy shows slight basal layer vacuolization, dermal edema and a superficial dermal perivascular lymphocyte and eosinophil infiltrate. No necrosis is present. (H&E, 200X). **b** Eosinophils (arrows) are present with lymphocytes around the superficial dermal capillaries fibrinoid necrosis of capillary walls, a sign of vasculitis, is not present. (H&E, 400X)

Table 2 Rash Treatment and Outcome

| Patient | Supportive Measures | Treatment | Total Steroid Duration | Duration of Rash | Targeted Therapy Re-initiation | Additional Therapies | Disease Status after Rash |
|---------|-----------------------|------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | IVFs | Dexamethasone 10 mg q6h inpatient then prednisone 1 mg/kg followed by extended taper outpatient | 42 days prescribed (however remained on steroids for entire duration of targeted therapy) | 39 days | Yes, D/T 44 days after rash onset On prednisone 10 mg daily | Temozolomide | Mixed response at 1 month, significantly worsened disease at 2 months |
| 2 | IVFs | Prednisone 150 mg daily inpatient followed by extended taper outpatient | 53 days | 37 days | Yes, D/T 39 days after rash onset On prednisone 10 mg daily | Ipilimumab Pembrolizumab CD40 agonist/ Pembrolizumab | Mixed response at 1 month, stable disease at 1 year, worsened disease at 18 months |
| 3 | IVFs | Methylprednisolone 50 mg daily inpatient followed by prednisone 60 mg daily with extended taper outpatient | 17 days after first rash onset For duration of targeted therapy after rash recurrence | 16 days | Yes, V/C (dose reduced) 24 days after rash onset Off prednisone Immediate fever and rash, held additional 13 days then restarted while on prednisone 30 mg daily | None | Mixed response at 1 month, improved disease at 4 months, worsened systemic disease at 8 months, worsened intracranial disease at 9 months |
| 4 | None | Prednisone 20 mg daily for 3 days, 10 mg daily for 3 days | 6 days | 12 days | Yes, V/C 13 days after rash onset Off prednisone Recurrence of rash after 1st dose, discontinued again Restarted 59 days after rash onset Immediate grade 4 allergic reaction to vemurafenib Tolerated D/T 166 days after initial rash onset when started with concurrent steroids | Temozolomide D/T Ipilimumab | Improved disease at 1 month, mixed response at 3 months (before temozolomide), worsened disease at 5 months (on temozolomide) improved response at 9 months (after initiation of D/T), worsened disease at 13 months |
| 5 | IVFs, Vasopressors | Methylprednisolone 70 mg BID inpatient followed by prednisone 60 mg daily with extended taper outpatient | 54 days at time of readmission for rash recurrence when tapered to prednisone 5 mg daily, prolonged taper again thereafter | 15 days | No | Temozolomide | Disease progression at 2 months (before temozolomide), worsened disease at 5 months |
| 6 | None | Prednisone 10 mg daily followed by extended taper | Ongoing (> 50 days) | 6 days | Yes, V/C 7 days after rash onset On prednisone 10 mg daily | None | No disease progression |

IVFs Intravenous fluids, V Vemurafenib, C Cobimetinib, D Dabrafenib, T Trametinib

introduction of vemurafenib-based TT combinations. These findings are consistent with other reports of adverse cutaneous responses manifesting within a similar timeline in patients treated with vemurafenib after exposure to nivolumab [10, 11] and ipilimumab [12]. Most of these reported cases used single agent vemurafenib without concurrent MEK inhibition following ICB. This is in contrast to our series and a series by another group [8] where the B-RAF/MEK combination was used, albeit with similar findings. For now, mechanisms dictating augmented toxicity with vemurafenib containing combinations following ICB remain unclear, which has prompted us to modify our clinical practice by incorporating dabrafenib instead of vemurafenib for B-RAF

inhibition when choosing TT combinations after disease progression on ICB.

Most of the patients had clinical features consistent with SIRS. In a subset of patients, these cutaneous adverse events were associated with a rise in makers of inflammation such as C-reactive protein (Table 1). It is notable to mention that in addition to other pro-inflammatory cytokines, one patient also had a high level of the soluble interleukin-2 receptor (IL-2R), a nonspecific marker of T-lymphocyte activation often used as one of the diagnostic criteria for hemophagocytic syndromes [13]. This could explain the constellation findings of SIRS with high a CRP, hypotension, and fever seen in our series. Similarly, in another report of two patients

with TT after ICB, one patient had a similar presentation of rash with SIRS within 8 days of starting V/C after ICB [14]. Although findings attributed to potential macrophage activation syndrome with D/T after ICB have been reported in the literature [15], no accompanying cutaneous features were observed. Thus a deeper understanding of the role of altered cytokine physiology during these adverse events may facilitate in better management strategies.

Given that none of our patients had clinical or histological features concerning for Stevens - Johnson syndrome (SJS) and a majority were noted to have disease progression, an attempt to restart TT (patients 1–4 and patient-6) was made within 1–8 weeks after the rash. We observed that delayed re-exposure to the treatment after completing a steroid taper resulted in rash reoccurrence whereas re-exposure with steroid overlap was not associated with rash reoccurrence in our case series. This again is suggestive of a persisting immune activation despite drug discontinuation, a feature commonly attributed to the prolonged pharmacodynamic activity of ICB which perhaps can be ameliorated using steroids when opting to re-challenge these patients with TT. Also, of the five patients who were restarted on TT, four were able to stay on it with good effect for >200 days after re-initiation. Thus the possibility of achieving clinically meaningful benefit on re-challenging these patients with TT needs strong consideration (Table 3).

Due to the clinical presentation and the pattern of the diffuse morbilliform rash, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome was considered a leading differential in four of our six patients. Our patients lacked the severe transaminitis, eosinophilia, and extended latency periods commonly seen in DRESS syndrome, but did have features that would support a diagnosis of “possible” or “probable” cases by RegiSCAR criteria [16], including fevers, facial swelling, and duration of the rash. Interestingly, this atypical pattern of DRESS syndrome, lack of eosinophilia and shorter latency periods for grade-4 rash, has been described in other series of patients receiving TT following ICB [8]. Nevertheless, a high index of suspicion for

SJS or toxic epidermal necrolysis (TEN) should be maintained in all patients presenting with rapid-onset, diffuse rashes after changes in drug therapy. Although two of our patients had mucositis, this was limited to the oral mucosa, and the remainder of the rash did not blister or desquamate which again did not support SJS. In cases such as these, a skin biopsy can be particularly helpful in predicting the clinical course.

Despite the extensive nature of the rash on clinical exam, the pathologic findings in the skin biopsies for our cases were relatively mild and primarily characterized by papillary dermal edema with a lympho-eosinophilic infiltrate (Fig. 3). This pattern of inflammation suggests a delayed hypersensitivity type reaction. None of the biopsies showed toxic epithelial changes or interface alterations suggestive of SJS/TEN, erythema multiforme-like drug reactions or vasculitis. In contrast, the biopsy from patient-2 displayed distinctive features of sub-epidermal vesicle formation and positive immunofluorescence studies supportive of an immunobullous disease. Given that patient 2 was on TT for a long duration without any CAEs, we believe that the use of an antibiotic in patient-2 for possible pneumonia (Table 1) may have worked in conjunction with the TT (D/T) to produce the dramatic clinical picture along with the cutaneous findings. In general, the scarcity of the inflammatory cells and lack of toxic or necrotizing changes in the cutaneous vessels and epithelium were unifying histopathologic features in our skin specimens.

An important point to note is the timeline of onset and severity of the CAEs. The median time to onset of rash in our series was 14.5 days. Development of a rash within 5–14 days is typical for a morbilliform or simple drug eruption; in contrast, patients with a systemic drug hypersensitivity eruption often have a more delayed presentation 3–6 weeks after drug initiation. Our patients had features of systemic hypersensitivity but presented earlier than might be expected for typical drug-induced hypersensitivity or DRESS syndrome. This seems distinct from the rash that patients have TT without history of prior immunotherapy in which the duration of medication exposure prior to rash onset is longer with less severe systemic symptoms. This could support the hypothesis that exposure to prior immunotherapy led to durable immune alterations which would then augment a hypersensitivity drug reaction caused by TT, thus explaining the more rapid onset and the severity of symptoms, a mechanism proposed by others too [14]. For now more pre-clinical data to identify molecular mechanisms linking ICB to TT that could drive these CAEs is required to support these claims.

Several trials currently underway are aimed at elucidating the utility of using a two-pronged approach of combining TT and ICB as well as sequencing these agents [4, 17, 18]. A highly anticipated trial looking into

Table 3 Practical Advice for Clinical Management

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- Consult dermatology and biopsy right away, photographs recommended to help document rash.
 - Consider obtaining CRP as surrogate for IL-6 as patients may present with SIRS.
 - Consider re-initiation of therapy after rash (at lower dose, with steroid overlap), particularly if no signs of SJS, biopsy appears benign relative to clinical rash, and patient was having a good response to the therapy or does not have alternate therapy options.
 - Consider avoidance of other stimulating medications or known activating medications such as amoxicillin, amoxicillin-clavulanic acid, allopurinol
-

the optimal sequencing of TT and ICB is the ECOG phase III study [19] estimated to have results reported by 2022. It is hopeful that the results of these trials will provide definitive information on the optimal strategy for sequencing of TT and ICB and thus could have significant implications on influencing treatment decisions in advanced B-RAF mutated melanoma in the near future.

In conclusion, our cases highlight the importance of maintaining a high index of suspicion for toxicities especially involving the skin when opting for strategies that involve sequencing of TT and ICB more so in the first two to 3 weeks of the switch. Findings from our cases show that these adverse clinical presentations with associated cutaneous findings tend to respond well to supportive measures and steroids. Also, depending on the disease status and the grading of the reactions, it may be reasonable to re-challenge select patients under strict supervision preferably with a steroid overlap even after rash resolution; keeping in mind that persisting immune activation from ICB may portend a high risk of rash reactivation despite several weeks of steroid use. Given the lack of prospective studies so far, most of our experiences with such agents administered either sequentially or in combination are guided by retrospective data similar to ours. Hence unraveling principles governing optimal sequencing or mechanisms contributing to potential toxicity patterns in patients receiving these treatments requires further understanding with prospective evidence.

Acknowledgements

Patients and their families.

Funding

No funding was required in the preparation of this manuscript.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

ARN and DF contributed equally to this paper. ARN was primarily involved in conceptualizing the study, manuscript writing and editing the tables/ Figs. DF was involved in patient data collection, creating tables/figures and editing the manuscript. CZ and PG were involved in providing important insights about the dermatological and pathological features of the patients as well as editing relevant sections of the manuscript. PG also provided pathology images for the paper. YW was involved in clinical care of some of the patients during their hospitalization as well as editing portions of the paper. PL was involved in the clinical care of some of these patients. FC was the oncologist involved in managing the patients, study conceptualization, writing and making necessary revisions to the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Appropriate consent for reporting patient data/images presented in this manuscript was obtained from the UNC IRB (IRB 18–0310).

Consent for publication

Individual patient consent was not applicable as no information in this article including the images can be categorized as identifiable.

Competing interests

The authors declare that they have no competing interests.

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Received: 28 October 2018 Accepted: 6 December 2018

Published online: 08 January 2019

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