# Drug-induced hypersensitivity syndrome like reaction with angioedema and hypotension associated with BRAF inhibitor use and antecedent immune checkpoint therapy

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***Key words:*** BRAF; BRAF inhibitor; CTLA4; dabrafenib; DIHS; DRESS; encorafenib; ICI; immune checkpoint therapy; immune related adverse effect; irAE; ircAE; oncoderm; PD1; PD-1; PD-L1; rash; vemurafenib.

## INTRODUCTION

Patients with BRAF-mutated malignancies, including advanced melanoma, brain, and thyroid cancers commonly receive targeted therapy with BRAF inhibitors (BRAFi).[1] Cutaneous adverse events are commonly (92%-95%) associated with BRAFi treatment.[2] Although most of these can be managed with supportive care, life-threatening reactions requiring drug cessation do occur.[2] Importantly, drug-induced hypersensitivity syndrome (DIHS)-like reactions during BRAFi treatment occur more often in the setting of prior immune checkpoint inhibitor (ICI) therapy, hypothesized to be a consequence of "immune priming".[3-5] In a series of metastatic melanoma patients receiving BRAF and MEK inhibition (n = 42) with or without prior ICI, for example, only those patients who had received ICI were at risk at developing DIHS-like reactions (n = 4).[4] Although DIHS can occur with ICI alone, it is uncommon (less than 2% of cutaneous reactions associated with PD-1 inhibition are grade 3 or higher), suggesting that the ICI + BRAFi treatment sequence may be unique in its propensity to cause a DIHS-like reaction.[6,7] To this end, we describe 5 cases of what we refer to as DIHS-like reaction (DLR) in patients who received BRAF inhibitors with preceding ICI therapy. Unique features of hypotension, angioedema, cytopenias, and oropharyngeal involvement were common, whereas eosinophilia and lymphadenopathy were absent on presentation.

*Abbreviations used:*

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|---|---|
| BRAFi: | BRAF inhibitors |
| DIHS: | drug-induced hypersensitivity syndrome |
| DLR: | DIHS-like reaction |
| ICI: | immune checkpoint inhibitor |
| TT: | targeted therapy |

## CASE SERIES

Five consecutive patients (2 men and 3 women; median age, 54 years; range, 41-71 years) with BRAFi-induced DLR and preceding ICI therapy were identified on retrospective chart review (Table I). Patients were only included in the review if they met the criteria for DLR as follows: DLR was diagnosed based on the typical cutaneous features of DIHS (morbilliform dermatitis, facial erythema and/or edema), clinical and laboratory-based evidence of systemic involvement, absence of alternative drug culprits, and recrudescence after re-challenge with BRAFi. All patients had no listed drug allergies prior to the DLR, except for patient 1 who reported a childhood penicillin allergy (unconfirmed). All had progression of metastatic BRAF V600E-positive malignancies during ICI treatment (ie, single or multiple agent PD-1, PD-L1, and/or CTLA-4 inhibitors) prompting initiation of combined BRAF inhibitor/MEK inhibitor (MEKi)-targeted therapy (TT). Three patients had metastatic melanoma, one had metastatic lung adenocarcinoma, and one had metastatic

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**Table I.** Clinical characteristics of DLR in patients after BRAF/MEK inhibition following ICI and their treatment and re-challenge response.

| Case No./ Sex/Age (y)/ disease | Prior ICI therapy (listed sequentially) | TT (days started after last ICI dose) | Onset of DIHS rash (days after starting TT) | Fever (Tmax in Fahrenheit) | Low BP* | RegiSCAR score | Mucosal symptoms | Angioedema signs and/or symptoms | Systemic involvement | Pathology | Response to steroids (days until rash resolution after starting systemic steroids) | Rebound symptoms with re-challenge to alternative BRAF/MEK inhibitor TT (clinical presentation) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Dabrafenib/ trametinib | Encorafenib/ binimetinib | Vemurafenib/ cobimetinib |
| 1/M/60s/ MPTC | Pembrolizumab | Dabrafenib/ trametinib (75) | 13 | Y (101) | Y (90s/60s) | 3 | N | Y (face, lips) | Hematologic (thrombocytopenia, lymphopenia), hepatic, renal | SPD with eosinophils, mild vacuolar interface dermatitis, mild dermal hemorrhage | Y (7) | Rash, fever, chills, hypotension (on prednisone 40 mg/day) | N/A | N/A |
| 2/F/40s/ MM | Ipilimumab, pembrolizumab | Dabrafenib/ trametinib (9) | 12 | Y (104) | Y (80s/50s) | 2 | Y (mild cheilitis and odynophagia) | Y (face, ear, periorbital, lips, neck, arms, hands) | Hematologic (thrombocytopenia, lymphopenia), hepatic, renal | N/A | Y (11) | N/A | <24H onset of rash, facial edema, fever, hypotension, transaminitis (on prednisone 40 mg/day) | Transient rash while undergoing slow desensitization initially with vemurafenib, then cobimetinib |
| 3/F/50s/ MM | Nivolumab, ipilimumab | Vemurafenib/ cobimetinib (37) | 9 | Y (103) | Y (80s/50s) | 3 | Y (severe odynophagia† and transient ocular pain) | Y (face, periorbital, neck, subjective throat swelling) | Hematologic (thrombocytopenia, lymphopenia) | SPD with eosinophils, mild dermal hemorrhage | Y (20) | Flu-like symptoms and leg weakness‡ | Flu-like symptoms | <24H onset of rash, nausea, vomiting, fever, hypotension (vemurafenib only, on 30 mg/day prednisone) |
| 4/F/70s/ MLA | Pembrolizumab | Dabrafenib/ trametinib (2) | 8 | Y (102) | Y (80s/ unknown at outside hospital) | 3 | Y (cheilitis, ulcerations in buccal mucosa and hard palate) | Y (facial, lip) | Hepatic | N/A | Unknown (no documented systemic steroids from outside hospital records) | <24H onset of rash, fever, hypotension, vomiting, fatigue (dabrafenib only) | N/A | N/A |
| 5/M/40s/ MM | Pembrolizumab, ipilimumab, nivolumab | Vemurafenib/ cobimetinib (concurrent with ICI) | 6 | Y (104) | Y (100s/70s) | 3 | Y (severe odynophagia) | Y (face, ear, periorbital, hands) | Hematologic (thrombocytopenia, lymphopenia), hepatic | SPD with eosinophils, mild vacuolar interface dermatitis, prominent papillary edema, mild dermal hemorrhage | Y (14) | Flu-like symptoms on prednisone 10-20 mg/ day | Flu-like symptoms on prednisone 15 mg/day | N/A |

*BP*, Blood pressure; *F*, female; *DIHS*, drug-induced hypersensitivity syndrome; *ICI*, immune checkpoint inhibitor; *M*, male; *MLA*, metastatic lung adenocarcinoma; *MM*, metastatic melanoma; *MPTC*, metastatic papillary thyroid cancer; *N*, no; *N/A*, not available/applicable; *SPD*, superficial perivascular dermatitis; *TT*, targeted therapy; *Y*, yes.

*Lower than baseline AND associated with receiving intravenous fluid resuscitation on admission.

†Also found to have thrush, treated with oral fluconazole and clotrimazole troches.

‡Preceded by initial TT causing DIHS.

papillary thyroid carcinoma. The median time-to-initiation of TT after the last dose of ICI was 23 days (range, 2-75 days) excluding patient 5, who received TT concurrent with ICI.

All patients developed a pruritic grade 3 (>30% body surface area) morbilliform dermatitis with prominent facial involvement and edema, accompanied by fever, malaise, and hypotension requiring intravenous fluids a median of 9 days (range, 6-13 days) after TT initiation (Fig 1). Three patients had odynophagia. Endoscopic evaluation in one patient showed desquamation and ulcerative lesions in the oropharynx, hypopharynx, and larynx; these resolved with supportive care. Patients who developed odynophagia or oral mucosal changes also had nausea, abdominal pain, vomiting and/or diarrhea at presentation. Clinical examination was notable for edema of the lips and/or extremities (Table I).

Eosinophilia and lymphadenopathy were absent at initial presentation. RegiSCAR[8] scores were low (2-3; possible DIHS). Hematologic (usually lymphopenia and thrombocytopenia) and hepatic involvement were most common, followed by renal involvement (Table I). Of note, due to the COVID-19 pandemic, patient 4 had her tests carried out approximately one week after her rash began with an unremarkable complete blood count at presentation (no differential) and interval development of neutropenia (1350 cells/$\mu$L) and mild eosinophilia (700 cells/$\mu$L) on day 13 of the rash. Viral reactivation was present in patients 4 and 5 (human herpesvirus 6-positive), and the true incidence is likely underestimated due to missing data. Histopathologic findings in skin biopsies showed superficial perivascular dermatitis with eosinophils and mild dermal hemorrhage. Mild interface change with rare dyskeratosis and dermal edema were variably present (Table I).

Most patients were successfully treated with cessation of TT and initiation of intravenous methylprednisolone (1-4 mg/kg/day) or prednisone (1 mg/kg/day). Patient 4 was hospitalized for hyponatremia and hypovolemia but did not receive systemic steroids, and her rash was managed with topical steroids and drug cessation. Patients (n = 4) who received systemic corticosteroids had a median time-to-resolution of the rash (typically concurrent with normalization of lab abnormalities) of 12.5 days from systemic corticosteroid start date (range, 7-20 days). Epinephrine pens were prescribed as rescue medications given the clinical features of anaphylaxis, but none of the patients in this series required epinephrine use.

Because BRAFi/MEKi represented the last-line cancer therapy in all cases, all patients were re-challenged with combination or single-agent alternative BRAFi/MEKi. Re-challenge with BRAFi led to rebound symptoms, often severe and within hours, in all patients (Table I). All patients permanently discontinued BRAFi due to DIHS features or other side effects except for patient 2 who, co-managed with Allergy and Immunology, successfully completed a slow inpatient desensitization with alternative BRAFi/MEKi.

## DISCUSSION

In this report, we characterize the unique clinical and laboratory features of DLR due to BRAFi when given sequentially after ICI, including faster onset (<2 weeks) than traditional DIHS (2-8 weeks) despite first-time exposure to drug.[8] The term "DIHS-like reaction" (DLR) acknowledges that the pathogenesis of DLR in these cases may be different than typical DIHS, particularly given the atypical clinical features and low RegiSCAR scores. These patients commonly exhibited hypotension, angioedema of nonfacial sites, and oropharyngeal mucosal involvement. Bone marrow involvement with multiple cytopenias and no lymphadenopathy were common features. Presence of type I hypersensitivity features (eg, hypotension and angioedema) and absence of eosinophilia in 4 of 5 patients in this case series and other reported cases,[4] again, likely reflects a unique mechanism of DIHS in the context of ICI priming.

The etiology of the unique clinical phenotype involving type I features in these cases is unclear, but we can make assumptions based on the common underlying Th2 precursor for type I and type IV hypersensitivity reactions. In carbamazepine-associated type IV drug hypersensitivity, drug-specific Th2 cells produce cytokines, including IL-5, IL-4, IL-10, and IFN$\gamma$.[9] More highly-differentiated Th2 cells produce higher levels of IL-5, which stimulates eosinophils,[10] and which could explain the longer period of drug exposure required for typical drug rash with eosinophilia and systemic symptoms/DIHS in comparison to BRAFi-induced DIHS following ICI. Indeed, T cells activated in vitro with CD3/CD28 beads and treated with BRAFi produce high levels of IL-13 but not IL-5.[11] IL-13 and IL-4, cytokines that are produced in higher levels by less-differentiated Th2 cells,[10] promote B-cell maturation and IgE class switching essential to type I hypersensitivity reactions.[12] Progression of disease during immunotherapy may select for patients with a Th2-deviated T-cell repertoire,[13] inadvertently selecting for patients who are more likely to experience BRAFi-associated DIHS with type I hypersensitivity features.

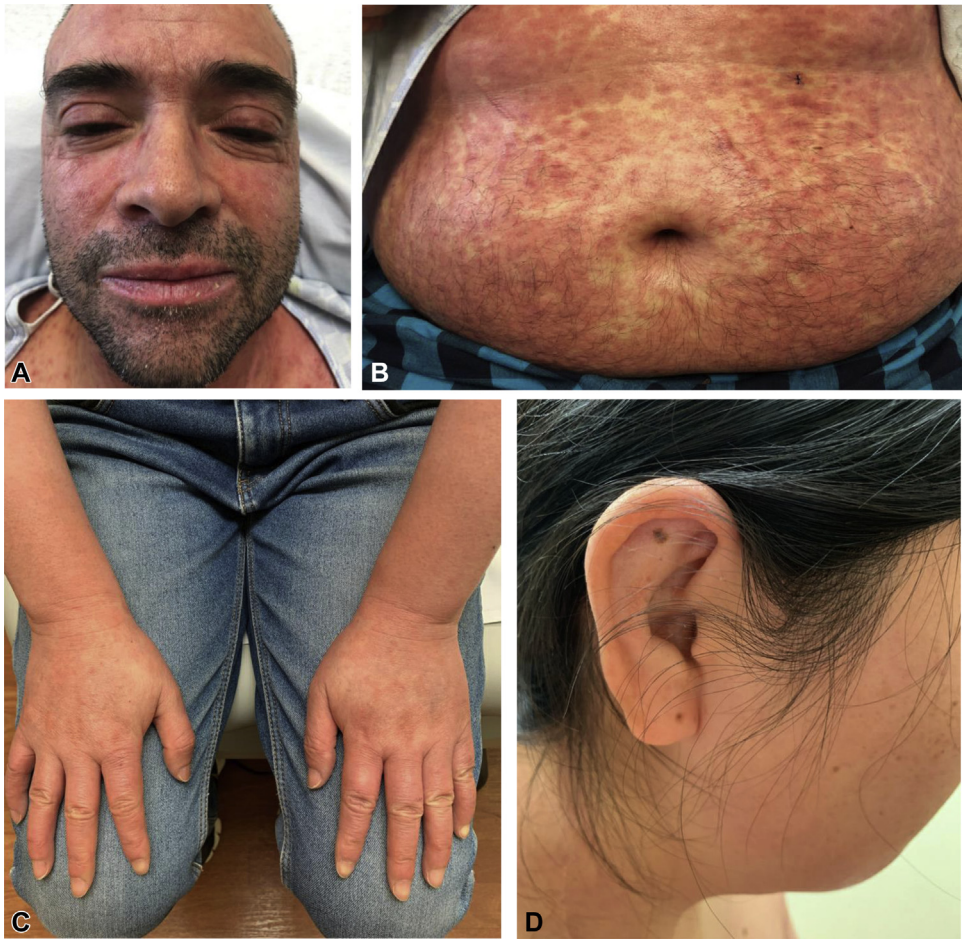


**Fig 1.** Marked facial, lip, and periorbital edema and erythema (**A**) and morbilliform eruption (**B**) in patient 5. Nonfacial angioedema of the upper extremities (**C**) and ear and facial erythema (**D**) in patient 2.

In terms of clinical recognition, it is important not to rely on RegiSCAR scores alone as all patients had low scores (2-3) despite having some typical DIHS features (eg, facial edema and morbilliform eruption). Recrudescence of DLR was rapid (within hours) upon re-challenge with BRAFi, even at lower doses. Patients improved quickly with BRAFi cessation and initiation of systemic and/or topical corticosteroids.

Patients receiving a higher number of ICI treatments tended to have a shorter time to onset of BRAFi DLR (Table I), supporting the immune-priming hypothesis that ICI exposure intensifies cell-mediated hypersensitivity.[3] Three patients had stereotactic radiosurgery preceding TT, which could additionally contribute to immune priming.[14] Attribution of DLR to BRAFi is favored based on numerous reports of DIHS/drug rash with eosinophilia and systemic symptoms to single-agent BRAFi and an infrequent incidence of MEKi related DIHS/drug rash with eosinophilia and systemic symptoms.[5] In addition, patients 2, 3, and 4 were all re-challenged with single-agent alternative BRAFi and experienced DLR rebound but tolerated MEKi without rebound. Importantly, BRAFi and ICI can both have side effects, including—but not limited to—rash, fever, malaise, and transaminitis.[15] However, as demonstrated by this cohort, the presence of angioedema, facial swelling, and hypotension in conjunction with other systemic symptoms is a unique presentation of DLR and distinct from BRAFi and/or ICI toxicity alone that becomes more exuberant on re-exposure and may require hospitalization for management.

Re-challenge was pursued shortly after DLR resolution due to limited treatment options for metastatic disease. During re-challenge, cross-reactivity among current FDA-approved BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) was common (Table I). Patient 2 underwent desensitization starting in the inpatient setting (2 mg to 60 mg of vemurafenib daily over 24 days) on prednisone

10 mg daily and reached the full dose (960 mg twice daily) after graded dose increases over 4 months, while receiving low-dose prednisone (5 to 10 mg daily). She also tolerated the addition of full-dose cobimetinib.

In summary, BRAFi-related DLR primed by ICI therapy may have a fast onset (<2 weeks) and present with life-threatening hypotension, angioedema, cytopenias, and oropharyngeal involvement, which could reflect a hybrid type I/IV hypersensitivity reaction. Clinical suspicion, with attention to sequence of anticancer therapies and recognition of facial erythema and edema, is critical for early intervention, as patients may need hospitalization support for hypotension and cytopenias. Because BRAFi can be last-line anticancer therapy for patients with metastatic disease, the decision to re-challenge may occur more frequently than with other drugs. Due to the potential for life-threatening DLR rebound and anaphylaxis, a re-challenge or slow desensitization should be considered in a monitored setting with multidisciplinary expertise to optimize patient safety.

**Conflicts of interest**

Dr Bernice Y. Kwong is a consultant for Genentech, Oncoderm, Happy 2nd Birthday. Moreover, she is member of the Advisory Board of Kyowa Kirin. No other conflicts of interest declared.

**REFERENCES**

1. Sanchez JN, Wang T, Cohen MS. BRAF and MEK inhibitors: use and resistance in BRAF-mutated cancers. *Drugs*. 2018;78(5):549-566.
2. Lacouture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist*. 2013;18(3):314-322.
3. Naqash AR, File DM, Ziemer CM, et al. 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. *J Immunother Cancer*. 2019;7(1):4.
4. Lamiaux M, Scalbert C, Lepesant P, et al. Severe skin toxicity with organ damage under the combination of targeted therapy following immunotherapy in metastatic melanoma. *Melanoma Res*. 2018;28(5):451-457.
5. Brégeon B, Bernier C, Josselin N, et al. Drug reaction with eosinophilia and systemic symptoms syndrome induced by combination of vemurafenib and cobimetinib in melanoma: a series of 11 cases. *J Am Acad Dermatol*. 2019;80(2):558-562.
6. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. *Curr Opin Oncol*. 2016;28(4):254-263.
7. Coleman EL, Olamiju B, Leventhal JS. The life-threatening eruptions of immune checkpoint inhibitor therapy. *Clin Dermatol*. 2020;38(1):94-104.
8. Kardaun SH, Mockenhaupt M, Roujeau JC. Comments on: DRESS syndrome. *J Am Acad Dermatol*. 2014;71(5):1000-1000.e2.
9. Naisbitt DJ, Britschgi M, Wong G, et al. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. *Mol Pharmacol*. 2003;63(3):732-741.
10. Upadhyaya B, Yin Y, Hill BJ, Douek DC, Prussin C. Hierarchical IL-5 expression defines a subpopulation of highly differentiated human Th2 cells. *J Immunol*. 2011;187(6):3111-3120.
11. Liu L, Mayes PA, Eastman S, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: Effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. *Clin Cancer Res*. 2015;21(7):1639-1651.
12. Ozdemir C, Akdis M, Akdis CA. T-cell response to allergens. *Chem Immunol Allergy*. 2010;95:22-44.
13. Dai M, Hellstrom I, Yip YY, Sjögren HO, Hellstrom KE. Tumor regression and cure depends on sustained Th1 responses. *J Immunother*. 2018;41(8):369-378.
14. Elazzazy S, Abu Hassan T, El Seid A, Jacob CM. Toxic epidermal necrolysis associated with antiepileptic drugs and cranial radiation therapy. *Case Rep Oncol Med*. 2013;2013:415031.
15. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol*. 2015;7(2):122-136.