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Treatment of a Delayed Hypersensitivity-like Reaction after Second-line Therapy with Dabrafenib-Trametinib: A Case Report

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Abstract Melanoma is the third most prevalent skin cancer with the highest mortality rate amongst skin cancers. Recent therapeutic developments have improved its treatment options, however significant toxicity can be a limiting factor. In this report, we describe a case of a rare, delayed hypersensitivity-like reaction after treatment with dabrafenib-trametinib as a second line therapy in a metastatic melanoma patient treated with pembrolizumab initially. A 62-year-old Caucasian male presented with a left axillary mass, which was found to be BRAF V600E positive malignant melanoma upon biopsy. He proceeded to have full axillary node dissection and was scheduled to receive adjuvant immunotherapy with pembrolizumab. However, the treatment was delayed by 3 weeks due to COVID-19. The patient developed subcutaneous metastases within that time. Although he was started on pembrolizumab, the metastases continued to progress. The patient then opted to begin dabrafenib-trametinib and was started on full dose therapy. After two weeks, there was significant reduction of metastases clinically. Two days after the follow-up, he presented to the emergency room with diffuse non-pruritic hives all over the body without any symptoms of angioedema. In addition, there was a sudden increase in size of the subcutaneous metastases. He was treated with 50 mg Benadryl and 50 mg prednisone with almost immediate resolution and discharged on prednisone. Dabrafenib-trametinib was temporarily discontinued. Due to the limited treatment options, the patient was carefully restarted on his dabrafenib-trametinib regimen with slow prednisone tapering. Patient has had an excellent response with complete resolution of his disease with no measurable lesions found on the latest CT scan. After a thorough literature search of OVID Medline + EMBASE, it was concluded that this is a rare presentation and only a few similar cases have been reported. Therefore, health care provider education and strategies for reintroduction of immunotherapy, as presented through a prednisone regimen in this case, is imperative for proper management of adverse events.

Keywords: *melanoma, adverse events, immunotherapy strategies, PD-1 inhibitor, BRAF/MEK inhibitor, case report*

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1. Introduction

Melanoma is a malignant and aggressive form of skin cancer arising from melanocytes in the skin. While melanomas are responsible for the most skin cancer related deaths worldwide, they only account for 5% of skin cancer diagnoses [1]. It can be categorized into four types: superficial spreading, nodular, lentigo maligna and acral lentiginous [2]. Diagnosis of malignant melanoma at an early stage has a good prognosis [3]. Primary treatment can be curative with surgical excision [3] and the advent of adjuvant treatments have improved patient outcomes [4,5,6,7]. For cases where patients present with metastatic disease, options have improved significantly over the last decade, however they are still limited in curative potential.

1.1. Adjuvant Therapy

After resection of a cutaneous melanoma, adjuvant therapy can be indicated based on a multitude of factors including stage at diagnosis, risk of recurrence, comorbidities and the preference of the patient [4]. Adjuvant therapy is generally recommended from Stage III disease, with the presence of lymph node involvement, onwards to Stage IV. Nivolumab, pembrolizumab along with BRAF inhibitors such as Dabrafenib/Trametinib, are the prevalent therapies used in adjuvant treatment.

Nivolumab and pembrolizumab are preferred for adjuvant checkpoint inhibitor immunotherapy [4] in comparison to

single agent ipilimumab. This is based on significant enhancement of RFS (Relapse Free Survival) and decreased toxicity. The 5-year progression free survival rates for combination vs ipilimumab (36 versus 8 percent, hazard ratio [HR] 0.42, 95% CI 0.35-0.51) and nivolumab alone vs ipilimumab (29 versus 8 percent, HR 0.53, 95% CI 0.44-0.64) were better [5]. In addition, the OS (overall survival) rates for both combined therapy and nivolumab alone were also superior to ipilimumab alone [5]. Pembrolizumab has been shown to improve 3-year RFS in the whole clinical trial population versus placebo (64 versus 44 percent, HR 0.56, 95% CI 0.47-0.68), and in patients with BRAF V600 mutated versus placebo (62 versus 37 percent, HR 0.51, 99% CI 0.36) along with wild type tumors versus placebo (62 versus 47 percent, HR 0.66, 95% CI 0.46-0.95) [8]. In patients with lymph node involvement, both nivolumab and pembrolizumab have been approved for adjuvant therapy use [4].

Almost 50% of cutaneous melanomas have an activating BRAF mutation, with V600E being the most common [2]. These targeted therapies along with immune checkpoint inhibitors displayed promising results, by prolonging overall survival and progression free intervals in comparison to standard chemotherapy [6]. The rapid tumor regression with decreased adverse effects, especially dermatologic, seen with combination targeted therapy has led to the replacement of single use BRAF inhibitors [6]. There are three different combinations of BRAF/MEK inhibitors: vemurafenib-cometinib, encorafenib-binimetinib and dabrafenib-tramenitib [6]. The combination of dabrafenib-trametinib improved 5-year RFS compared to placebo (52 versus 36 percent; hazard ratio [HR] 0.51, 95% CI 0.42-0.61), 5 year distant metastasis-free survival, (65 versus 54 percent, HR 0.55, 95% CI 0.44-0.70), and 3 year OS (86 versus 77 percent; HR 0.57, 95% CI 0.42-0.79) [7].

1.2. Metastatic Therapy

The development of immunotherapy through immune checkpoint inhibitors opened doors towards new possibilities of treatments, beginning with ipilimumab; an anti- cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody approved for melanoma in 2014 [2]. In the phase III study of adjuvant ipilimumab E1609 trial, patients were assigned to different dosing regimens (10 or 3 mg/kg) of ipilimumab and compared to IFN-alpha [9]. Ipilimumab at the 3mg/kg dose had an improved OS compared to high dose IFN-alpha, and similar RFS [9]. After ipilimumab, came the anti-programmed cell death 1 (PD-1) antibodies, pembrolizumab and nivolumab [2].

Here we present a case of a delayed hypersensitivity-like reaction in a patient with metastatic melanoma treated with dabrafenib-trametinib as a second line agent post pembrolizumab.

2. Case Report

A 62-year-old Caucasian male presented with a mass in the left axilla in January 2020. Physical exam showed a palpable mobile axillary mass with no skin involvement. There were no pigmented lesions, visible subcutaneous metastases, in-transit lesions, or any other significant findings on clinical examination. Biopsy of the mass confirmed BRAF V600E positive malignant melanoma. He had no previous history of melanoma, and no primary lesion was identified. Other relevant medical history includes previous history of squamous cell carcinoma of the left leg completely excised in 2018. He also had a history of dyslipidemia. The patient was taking Vitamin C and D, lycopene, glucosamine and crestor (rosuvastatin). A Magnetic Resonance Imagining (MRI) scan of the head was clear. A Computer Tomography (CT) of the chest abdomen pelvis (CAP) scan showed a prominent right hilar lymph node, left axillary mass and no other metastases. A Positron Emission Tomography (PET) scan showed no uptake of radioactive drug tracer outside of the axilla.

The patient was presented with neoadjuvant clinical trials or surgery with adjuvant treatments. He opted to undergo surgical excision with adjuvant treatment. In February 2020, a left axillary dissection was performed, and pathology revealed 4 out of 40 lymph nodes involved with malignant melanoma, with the largest deposit being 55 mm with extra nodal extension (ENE). In terms of adjuvant therapy, dabrafenib-trametinib, and single agent immunotherapy (nivolumab or pembrolizumab) were discussed. The patient opted to be treated with pembrolizumab. However, before treatment could begin, the COVID-19 pandemic initiated a lockdown in Ontario, Canada. Due to the restrictions, the patient decided to wait for a few weeks. In first week of April 2020, the patient presented with a new right axillary mass and multiple subcutaneous lesions on the trunk in keeping with subcutaneous metastases. Now, the option of combination immunotherapy and clinical trials were discussed along with the other options discussed previously. The patient chose decided on single agent immunotherapy.

Pembrolizumab was then started in mid-April 2020. The subcutaneous lesions on the trunk seemed to be stable in most locations and then progressed slowly in some areas for the first six weeks raising suspicion for pseudo progression. However, a right axillary mass was seen to progress rapidly even after two treatments. The mass was still mobile but with erythema of the overlying skin. This right axillary mass was resected in the beginning of June 2020. Pathology confirmed the presence of 45 mm tumor deposit with necrosis. Two further doses of pembrolizumab were given, with the last dose in mid-July 2020. At this point subcutaneous nodules on trunk also showed progression. This progression was confirmed on CT with additional peritoneal metastases (See Figure 1 and Figure 2).

The patient was then referred for clinical trials as there was an option for the addition of a CTLA-4 inhibitor to the current pembrolizumab regimen. However, the patient chose to proceed with second line dabrafenib-trametinib instead. During this time, he was also noted to have persistent hypertension and was started on hydrochlorothiazide in July 2020.

Full dose dabrafenib-trametinib (Tafinlar 150mg 2x daily and Mekinist 2mg) was initiated in September 2020 (Table 1). Cardiac assessment showed left ventricular hypertrophy on electrocardiogram and echocardiogram. On day 14, outpatient assessment showed a grade 1 self-limited febrile illness. The subcutaneous metastases showed clinical improvement by almost 50%. On day 17,

the patient presented to the emergency room with diffuse, non-pruritic hives all over the body, along with facial and lip swelling without tongue or throat involvement. He also reported excessive swelling, discomfort, and pain at the site of subcutaneous metastases. The patient's vitals were normal. He was given 50 mg per os (PO) Benadryl and 50 mg PO prednisone. Symptoms completely resolved in a few hours. He was discharged with a prescription for 50 mg prednisone and an epi-pen, and dabrafenib-trametinib therapy was discontinued. On day 18, the patient was followed up by the oncologist through the telephone. He reported no further issues and a significant improvement in the subcutaneous metastases. The patient was prescribed Pantaloc for gastric protection. In addition, a tapering of prednisone was initiated as outlined in Table 1. On day 39, dabrafenib was restarted at the full dose while on prednisone at 20 mg daily. On day 43, full dose trametinib was reintroduced with prednisone continued at 20 mg. During this time subcutaneous nodules, although still palpable, were significantly improved.

He was continued on treatment with a slow tapering of prednisone and showed persistent improvement in lesions. No further hives were noted. He did report two episodes of chills and rigors without fever on day 90 and 91. These episodes were resolved with acetaminophen 325 mg PO. This was while being on 10 mg prednisone. There was no other significant toxicity. CT CAP on day 92 reported near complete resolution of subcutaneous and peritoneal metastases. Clinical exam on day 102 showed complete resolution of subcutaneous metastases. Most recent CT in January 2022 showed complete resolution of disease (See Figure 3 and Figure 4).

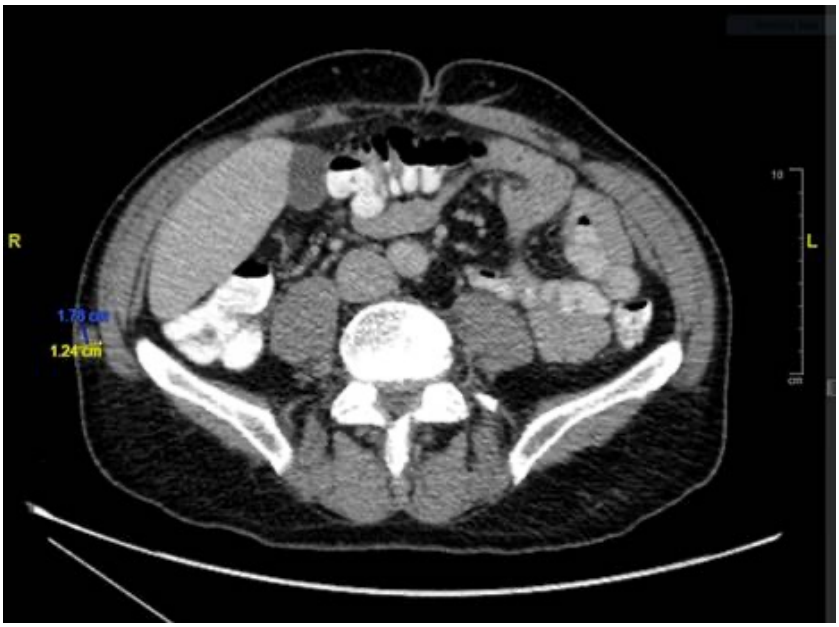

Figure 1. CT scan July 2020 demonstrating a nodule in the right lateral abdominal wall measuring 1.24 x 1.78 cm. Indicative of subcutaneous metastases. There are also omental nodules (not pictured) consistent with metastasis.

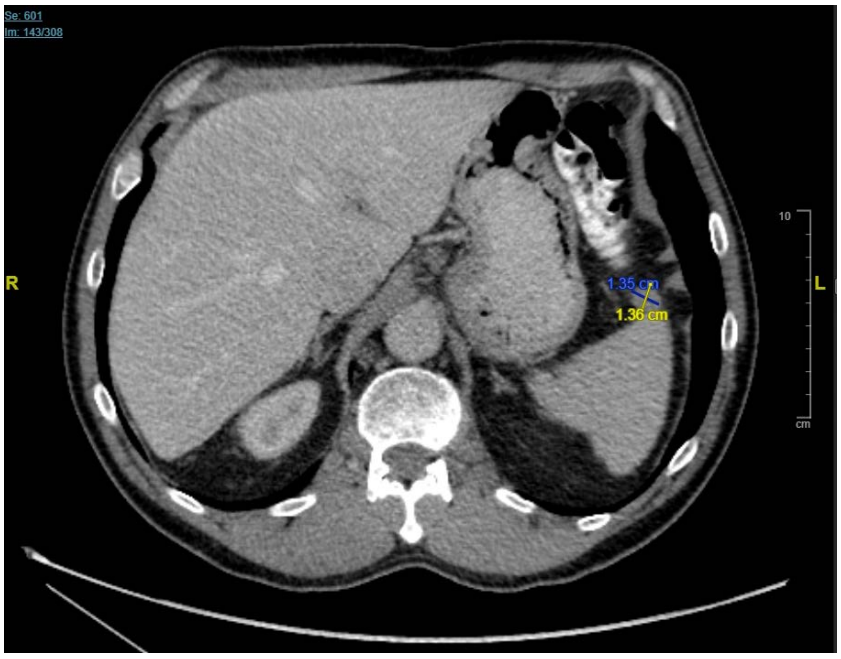

Figure 2. CT scan July 2020 shows a nodule measuring 1.36 x 1.35 cm anterior to the spleen. Findings are consistent with metastasis.

Table 1. Timeline of events after dabrafenib/trametinib administration

Day	Event
0	Dabrafenib/Trametinib administered
14	Outpatient assessment showed grade 1 self-limited febrile illness
17	Patient presented to ED
18	Telephone follow up by oncologist
33	Prednisone tapered to 30 mg
39	Restarted dabrafenib full dose, prednisone tapered to 20 mg. Patient was observed in the clinic for 8 hours
43	Started trametinib full dose, prednisone continued at 20 mg
53	Prednisone tapered to 15 mg
74	Prednisone tapered to 10 mg
96 - 180	Prednisone tapered to 5 mg for 2 weeks. Afterwards, switched to 5 mg every other day then twice a week completely stopping prednisone on day 180.

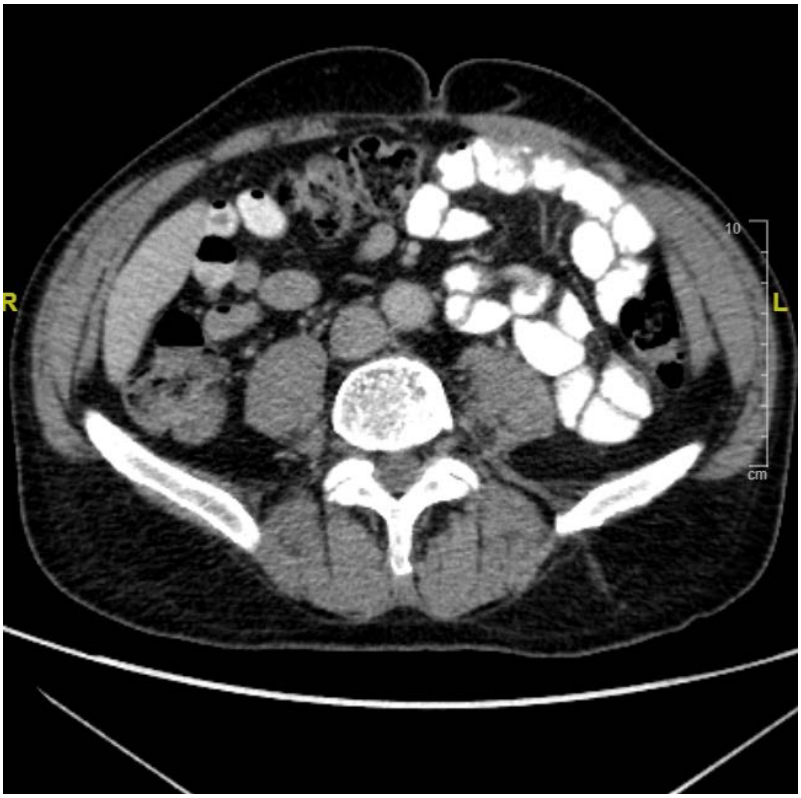

Figure 3. CT Scan January 2022 shows no free fluid and no lesions. No abnormalities found in soft tissues or abdominal wall.

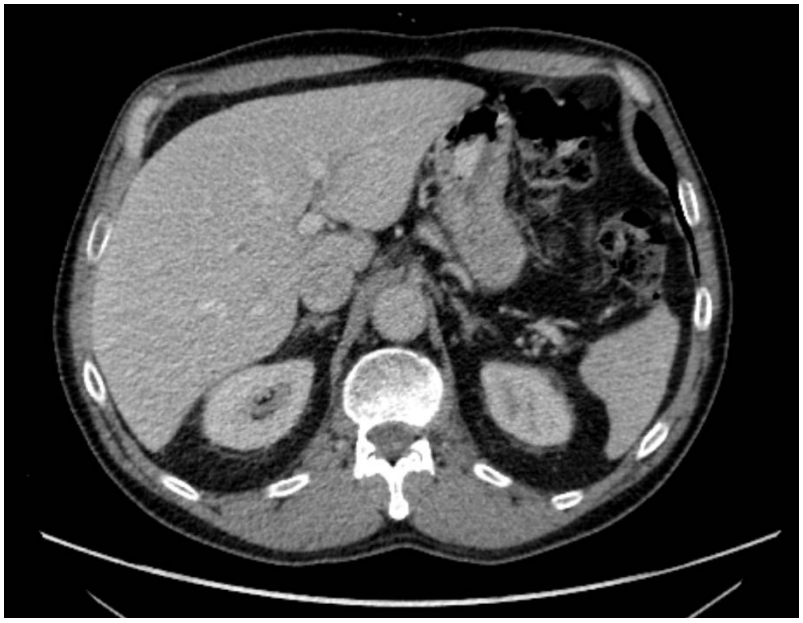

Figure 4. CT Scan January 2022 shows no free fluid and no lesions. No abnormalities found in soft tissues or abdominal wall.

3. Discussion

True hypersensitivity reactions, although rare, can significantly limit patients' treatment choices especially in oncology where options are limited to begin with. Multiple systems can be involved, with the respiratory and integumentary systems being some of the most commonly affected [10]. In our case, a delayed hypersensitivity-like reaction was observed in a patient who was initially treated with pembrolizumab and then developed symptoms 17 days after dabrafenib/trametinib administration.

Cross reactivity in immunotherapies is an elusive subject. Not much literature exists on the explanation of why there was a delayed hypersensitivity reaction to dabrafenib-trametinib administration after initial treatment with pembrolizumab. One possible theory could be allergy to the non-medicinal capsule of dabrafenib. It contains magnesium stearate which has been reported to cause allergic reactions with urticaria [11]. However, there were no overlapping ingredients between pembrolizumab and dabrafenib/trametinib. Dabrafenib has had reports of cutaneous adverse events, however, these are usually reduced when combined with a MEK inhibitor such as trametinib [12]. There is still a possibility that this was a delayed reaction to dabrafenib/trametinib itself.

Reports in preclinical studies have shown that BRAF inhibitors and MEK inhibitors can enhance immunotherapy through different mechanisms. Firstly, BRAF inhibitors can improve antigen presentation, increase T cell recognition of tumour antigens, increase melanoma antigen expression and also decrease immunosuppressive cytokines secretion from tumour cells [13,14]. Within the tumour, MEK inhibitors increase CD8+ T cells and also increase tumour antigen presentation [13]. Interestingly, PD-1 inhibitors such as pembrolizumab and nivolumab have a long half-life ranging from 12-22 days [15,16]. Introducing BRAF/MEK inhibitors in patients with prior exposure to immunotherapy, specifically PD-1 inhibitors, can lead to the modulation of the tumour microenvironment and cause immune related adverse events months after exposure [17]. This could be a possible explanation for the scenario presented in our case.

A literature search of Embase + OVID MedLine of "((skin or melanoma) and immunotherapy and hypersensitivity and mechanism).af." revealed 239 articles, and 220 after deduplication. Out of these, 6 were relevant to read for explanations on mechanism behind the reaction seen in our patient. Another search in the same databases ("(BRAF and hypersensitivity).af.)", revealed 106 articles, and 11 of them were relevant to our case. However, after review of these 17 combined articles, we concluded that this was a rare presentation. A similar case that exists in the literature was reported in 2017 by Fujimara et al [18]. They reported a case of exudative erythema multiforme caused by a type IV delayed hypersensitivity reaction to dabrafenib monotherapy after nivolumab. Their clinical and histopathological findings were similar with viral exanthema, leading them to believe that this could have been a viral reactivation [18,19]. In our patient, the lesions resolved completely within hours of administering Benadryl and prednisone and we were unable to obtain pictures or a biopsy.

4. Conclusions

We demonstrated a case of successful reintroduction of dabrafenib-trametinib in a patient with possible delayed hypersensitivity reaction with significant clinical benefit. With the increasing incidence of melanoma and the use of checkpoint and BRAF inhibitors, drug reactions will be more commonly encountered. Therefore, physician education about these rare presentations and side effects is of utmost importance for patient management. Treatment options for patients with melanoma, while improved, can be severely limited by toxicities. Understanding how to properly manage adverse events when toxicities arise is essential for optimal patient care. In this case, reintroduction of dabrafenib-trametinib allowed the patient to have complete resolution of the metastases. With careful reintroduction we were able to preserve a line of effective treatment for the patient; one that he continues to benefit from. As of January 2022, the patient continues on Dabrafenib and Trametinib and maintains his response to treatment.

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Statement of Competing Interests

The authors declare there are no competing interests.

List of Abbreviations

RFS (Relapse Free Survival)
OS (Overall Survival)
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
Programmed cell death (PD-1)
Magnetic Resonance Imagining (MRI)
Computer Tomography (CT)
Chest abdomen pelvis (CAP)
Positron Emission Tomography (PET) scan
Extranodal Excision (ENE)
Per os (PO)

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