

Anaphylaxis-like reaction to anti-BRAF inhibitor dabrafenib confirmed by drug provocation test

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The combination of BRAF and MEK inhibitors is a standard therapeutic option for patients with metastatic melanoma with BRAF-mutated tumors. This type of targeted therapy improved patient survival, having a manageable toxicity profile. Nevertheless, potentially life-threatening severe toxicity as anaphylaxis-like reactions was observed in two reported cases. No confirmatory testing was performed for these two patients. We report a case of anaphylactic reaction to the BRAF inhibitor dabrafenib administered as a first-line treatment. The clinical picture is different compared with the reported cases, with the main life-threatening symptom being severe hypotension. An important feature of our case report is the diagnostic assessment by drug provocation test, which is considered the 'gold standard' investigation for the diagnosis of drug hypersensitivity. Additionally, serum tryptase levels were assessed, and the basophil activation test has been performed as an in-vitro diagnostic test. Elements in favor of both IgE-mediated and non-IgE-mediated reaction were observed, which is suggestive of a complex

pathomechanism. This can be evocative for the heterogenous clinical manifestation of the immediate hypersensitivity reactions to BRAF inhibitors. The mechanisms responsible for the reactions should be investigated in future molecular and cellular studies. *Melanoma Res* 00:000–000 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

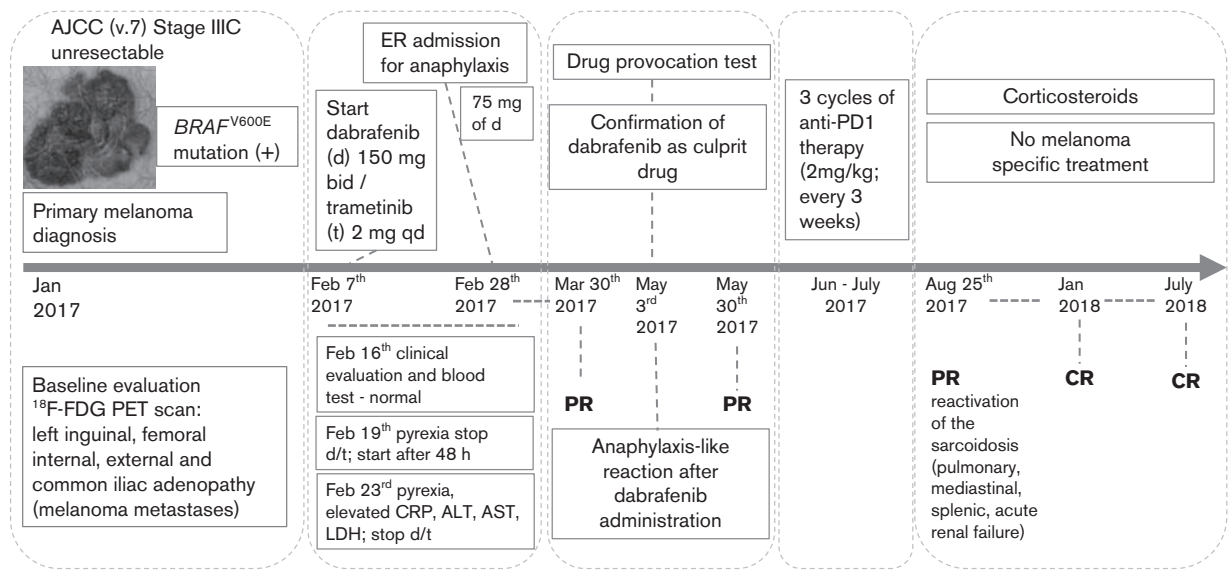
Targeted therapy with small-molecule BRAF inhibitors (dabrafenib, vemurafenib, and encorafenib) in association with MEK inhibitors (trametinib, cobimetinib, and binimetinib) and immune checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab) is the standard of care for patients with metastatic melanoma [1]. The presence of tumor-activating *BRAF*^{V600} mutations (40–50% of advanced melanomas) is a prerequisite for initiating targeted therapy for patients with metastatic melanoma [2,3]. These mutations lead to the constitutive activation of the mitogen-activated protein kinase pathway (MAPK), driving melanoma proliferation and survival [4,5]. Both targeted and immunotherapy improved patient survival with manageable toxicity [1]. Nevertheless, severe toxicity as anaphylaxis has been described with the new therapies as in the case of classical chemotherapeutics [6–9]. Anaphylaxis is the most severe type 1 allergic reaction, potentially life-threatening and requiring urgent medical intervention [10,11]. The key triggers are food, drugs, and stinging insects. Drugs and Hymenoptera venom are the most common in adults, whereas food is the most frequent cause in children [6,9,11,12]. We report the first case of anaphylactic reaction to the BRAF inhibitor dabrafenib in a

first-line setting for which confirmatory diagnostic testing has been performed by drug provocation test and basophil activation test.

Case report

A 59-year-old male patient presented with a primary melanoma of the left thigh in January 2017 (Fig. 1), which had high-risk characteristics for relapse: Breslow 4.5 mm, ulceration, and 10 mitoses/mm². The initial diagnostic workup showed left inguinal and femoral adenopathy as well as left internal, external, and common iliac enlarged lymph nodes, highly suspected to correspond to melanoma metastases on fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) PET scan. Additionally, the *BRAF*^{V600E} mutation was identified in the tumor tissue using NGS (Cancer Panel on the Ion Torrent platform, Thermo Fisher Scientific, Waltham, Massachusetts, USA). The multidisciplinary decision was to initiate treatment with systemic therapy using targeted therapy as first line (in the detriment of immunotherapy) owing to the patient history of autoimmune diseases. The history of the patient includes active sarcoidosis in 2009, treated with corticosteroids and methotrexate until 2015; Hashimoto's thyroiditis (hypothyroidism treated by levothyroxine monotherapy for thyroid hormone replacement); and

Fig. 1



Timeline of patient's clinical course. Clinical image for the primary melanoma is shown at diagnosis and baseline evaluation. Time is shown on the x axis and the tumor response is indicated at every ¹⁸F-FDG evaluation. Each distinct time interval (targeted therapy, no treatment, immunotherapy, and no specific melanoma treatment, correspondingly) is shown in rounded rectangle with dashed lines. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete remission; d, dabrafenib; ER, emergency room; ¹⁸F-FDG, fluorine-18-fluorodeoxyglucose; LDH, lactate dehydrogenase; PR, partial remission; q.d., daily

chronic renal failure. The patient had no history of mastocytosis, angioedema, or/and urticaria.

The treatment with dabrafenib and trametinib was started on 7 February 2017 at the standard dose of dabrafenib 150 mg, twice daily and trametinib 2 mg, daily. The first clinical and biological control at 1-week interval was normal, with no adverse events present at this time point. The medication was interrupted for 48 h during the second week of treatment owing to the occurrence of fever (the most common adverse event for this type of therapy). When the medication was resumed, the fever reappeared in the first 24 h, and the blood test revealed toxicity with C-reactive protein at 82 mg/l and abnormal hepatic tests (elevated alanine aminotransferase: 1.2 N, aspartate aminotransferase: 2 N, and lactate dehydrogenase: 1.6 N). After toxicity resolution, the treatment was once again resumed after one week on 28 February 2017. The patient took only one dabrafenib capsule of 75 mg and 1 h later presented with abdominal pain, diarrhea, erythroderma, and malaise. When the paramedics arrived at the patient's home, his blood pressure was 40/30 mmHg with pulse rate of 105 bpm and oxygen saturation of 80%. An anaphylactic shock was suspected; thus, the patient received intramuscular epinephrine: 0.5 mg, intravenous methylprednisolone: 125 mg, and intravenous colloids: fluid. The patient was admitted at the nearest hospital, and at admission, his blood pressure was improving (68/45 mmHg), but he presented peripheral cyanosis and cold extremities owing to major vasoconstriction and his abdomen was very painful at

the clinical examination. A full blood test panel showed at this time point (90–120 min after symptoms onset) a normal C-reactive protein, normal hepatic tests, and a tryptase level of 30.5 µg/l (normal range: 1–14 µg/l); the total IgE levels were also higher than the normal limit (251 kU/l; normal range <100 kU/l). The main symptom was very severe hypotension requiring large-volume intravenous fluid replacement. The patient recovered during the following hours. Additionally, the echocardiography and serum troponin T were normal excluding cardiac toxicity of the drug.

The later standard diagnostic workup comprised food allergy skin prick and ImmunoCAP ISAC (Thermo Fisher Scientific; miniaturized immunoassay platform for the measurement of IgE antibodies to a fixed panel of 112 components from 51 allergens). These tests showed negative results. The legal regulations of the hospital pharmacy did not allow the preparation of dabrafenib and trametinib for drug hypersensitivity testing. Therefore, a special request was sent to the company producing the drugs to provide us with soluble forms to perform the diagnostic tests, but the delay to receive the drugs was at least 6 months. Thus, the multidisciplinary decision was to perform an oral provocation test owing to the necessity of confirming the dabrafenib as the culprit drug for the patient's anaphylactic reaction. This was mandatory to enable a final decision regarding the future administration of these drugs in the eventuality of metastatic disease progression. On the day of the oral provocation test,

trametinib was administered first starting with 0.5 mg, and 2 mg was administered 30 min later. No reaction was observed during the following 2 h. Then the first dose of 50 mg of dabrafenib was administered followed by 75 mg and 50 mg during an interval of 2 h. The patient developed an anaphylactic-like reaction 1 h after the last dabrafenib administration. An increase in the level of tryptase compared with his baseline levels was observed (8.28 µg/l at 50 min and 10.7 µg/l at 2 h after symptoms onset (normal range <8.23) with normalization at 6.56 µg/l the next day). The patient developed severe hypotension (requiring large-volume intravenous fluid replacement) with tachycardia and nausea. He received intramuscular epinephrine 0.5 mg, intravenous methylprednisolone 80 mg, and intravenous fluid replacement. Because of persistent hypotension, the patient was kept under observation in the ICU for 4 h. He recovered without any sequelae. When the soluble forms of the dabrafenib and trametinib were provided 6 months later by the company, the basophil activation test was performed, with negative results for both drugs (negative control: 3.1% activated basophils, positive control: 37.8%, trametinib: 3.1%, and dabrafenib: 3.8%).

The first two follow-up ¹⁸F-FDG PET scans after stopping dabrafenib and trametinib therapy showed partial response, and anti-PD1 therapy was started as second line 4 months after targeted therapy was stopped (Fig. 1). After three cycles of anti-PD1 therapy, reactivation of the sarcoidosis was observed involving lungs, mediastinum, spleen and kidney with installation of acute renal failure). This adverse event was well controlled under corticosteroids oral therapy. At the next follow-up, the patient showed complete response, and he remains in complete remission 18 months after targeted therapy onset as first line and 1 year after all melanoma-specific treatments were stopped.

Discussion

Drugs are the most common cause of anaphylaxis in adults [12], and the number of anaphylactic reactions is increasing owing to the increased number of new drugs approved for the treatment of chronic diseases such as cancer [7]. Important changes in the landscape of cancer treatment were observed with the introduction of monoclonal antibodies and small-molecule-specific inhibitors. This is the case as well for the treatment of metastatic melanoma with the introduction of immune checkpoint inhibitors and the small-molecule BRAF inhibitors (dabrafenib, vemurafenib, and encorafenib) associated with MEK inhibitors (trametinib, cobimetinib, and binimetinib) [1]. The association of BRAF and MEK inhibitors is restricted to the BRAF-mutated patients, which represents 40–50% of the patients with metastatic melanoma [13]. We report the case of a patient with anaphylaxis specific symptoms after dabrafenib intake, which was confirmed by drug provocation test. Two

additional cases of type I hypersensitivity reactions are reported in the literature for the BRAF inhibitor vemurafenib [14,15]. The first case reported is peculiar because the patient developed first a delayed-type hypersensitivity reaction (generalized maculopapular rash), which resolved under oral corticosteroids. This was followed by an immediate reaction (erythroderma, dyspnea, and vomiting after 6 h from first dose intake), requiring epinephrine, corticosteroids, and antihistamines administration when treatment was resumed 1 month later [14]. The second case is particularly interesting because the patient developed similar symptoms when vemurafenib was changed to dabrafenib [15]. The patient developed generalized urticaria, facial, and throat angioedema 30 min after vemurafenib intake, and 2 weeks later, when dabrafenib was introduced, the patient developed the same symptoms after the first dose. In both situation, epinephrine administration was not necessary; the patient recovered after dexamethasone and diphenhydramine. The characteristics of the first case is suggestive of a non-IgE-mediated reaction (time of symptoms onset 6 h), whereas the second is evocative for IgE-mediated reaction. No confirmatory testing was performed for these two patients.

An important feature of our case report is the diagnostic assessment by drug provocation test, which is considered the ‘gold standard’ investigation for the diagnosis of drug hypersensitivity [16,17]. For our patient, the index event can be suggestive of an IgE-mediated reaction (time of symptoms onset 1 h after dabrafenib intake), and the symptoms (abdominal pain, diarrhea, erythroderma, and severe hypotension) meet the EAACI criteria for anaphylaxis [11]. An additional argument for a mast cell-mediated reaction is the increase in the serum tryptase level for both the index event and drug provocation test. However, for the provocation test, the time of symptoms onset and the dose of dabrafenib administered are more suggestive for a non-IgE-mediated reaction though. Additionally, the negative BAT testing can be an element for a mechanism that is not mast cell mediated, though a false negative cannot be excluded.

The case reported in our manuscript and the two additional cases described in the literature illustrate the heterogeneous clinical manifestation for immediate hypersensitivity reactions to BRAF inhibitors. The mechanisms responsible for the reactions should be investigated in future molecular and cellular studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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