Early-Onset Vemurafenib-Induced DRESS Syndrome

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Key Words
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Abstract
Vemurafenib is a BRAF inhibitor indicated in metastatic or unresectable melanoma in patients with BRAF mutations. Vemurafenib is frequently toxic, but the toxicity is often not serious. The third case of vemurafenib-induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is reported herein. The case is unusual in that the onset was early, with symptoms emerging as of day 8 of treatment. Treatment of DRESS syndrome is not currently based on precise recommendations, but systemic corticosteroid therapy is effective in serious cases. Severe toxidermias under vemurafenib are exceptional; immediate discontinuation of treatment upon diagnosis is imperative. Switching from vemurafenib to dabrafenib then seems to constitute an interesting therapeutic alternative, since its efficacy is the same but with fewer cutaneous adverse reactions. This case highlights the importance of awareness of the risk of DRESS syndrome associated with vemurafenib and monitoring for warning signs from treatment initiation.

Introduction
Vemurafenib is a BRAF kinase inhibitor indicated in the treatment of metastatic or unresectable melanoma in patients with the BRAF V600E mutation. Vemurafenib frequently induces cutaneous toxicity which mainly consists in phototoxicity, follicular keratosis, hyperkeratosis on weight-bearing areas, appearance of keratoacanthoma and squamous-cell carcinoma, and maculopapular rash of mild to moderate severity. A case of drug rash with eosinophilia and systemic symptoms (DRESS) induced by vemurafenib is reported herein.

Observation
A male patient, aged 65 years, with stage T3bN2bM0 (IIIC) melanoma (7th edition of the AJCC cancer staging manual [1]) was included in a double-blind trial to evaluate the efficacy of vemurafenib (investigational treatment) versus placebo as post-lymph node curettage adjuvant therapy. The BRAF V600E mutation was evidenced on the primary melanoma and an invaded lymph node. The patient did not have any other medical or surgical history, and there was no other drug intake. Vemurafenib was prescribed at a dosage of 960 mg b.i.d. combined with a 50+ sunscreen to be applied twice daily, a cleansing gel and a moisturizing cream. On day 8 after treatment initiation, a grade 1 (CTCAE, version 4) diffuse maculopapular eruption predominating on the photo-exposed areas appeared. Treatment was continued, and the patient was reminded of the instructions for photoprotection. However, the eruption gradually exacerbated and spread to all the skin. No other drug had been introduced. On day 21, the patient presented with erythroderma (fig. 1) with pustules at the axillary and inguinal skin fold level, facial edema (fig. 2), cheilitis, hyperthermia (40°C) and axillary lymphadenopathies measuring more than 1 cm. Given the negative course (CTCAE, version 4: grade 3), vemurafenib was immediately discontinued. Laboratory tests showed hepatic cytolysis with serum glutamic oxalacetic transaminase >7XN cytolysis, eosinophilia (3.670 × 10⁹/l) and acute renal failure (serum creatinine: 175 μmol/l). PCR did not identify any viral reactivation (HSV, EBV, CMV, HHV-6, HAV, HBV, HCV, HEV, HIV). Skin biopsy enabled ev-
idencing loose lymphoid infiltration of the papillary dermis predominating around the vessels, without eosinophilia, resulting in the conclusion that the lesions were little specific inflammatory lesions. DRESS syndrome was diagnosed according to the RegiSCAR international consensus criteria [2] with a score of 8 [fever >38.5°C: 0 point, enlarged lymph nodes: 1 point, eosinophilia: 2 points, skin rash extent >50%: 1 point, distribution suggesting DRESS: 1 point, involvement of 2 organs (kidney and liver): 2 points, and evaluation of other potential causes negative: 1 point]. Oral corticosteroid therapy was initiated at a dosage of 1 mg/kg, i.e. 80 mg daily, and the cutaneous condition and laboratory test results normalized within 1 month. Corticosteroid therapy was tapered to discontinuation over 1 month. Ten months after vemurafenib discontinuation, the patient did not experience any melanoma recurrence in the absence of any other treatment. Lactate dehydrogenase was then 3.47 µkat/l. The patient remained in malignant remission for 10 months and then experienced recurrence at the left inguinal level. The patient is currently treated with ipilimumab.

Discussion

The third case of vemurafenib-induced DRESS syndrome is reported herein. The case is very unusual in light of the early onset, only 8 days after treatment initiation. In general, DRESS syndrome appears in the 2 months following therapy initiation. In the other 2 cases of induced DRESS previously reported in the literature, lesion onset occurred early but later than in the present patient. The first case [3] consisted in a female patient, aged 80 years, with DRESS syndrome appearance 3 weeks after vemurafenib initiation. The second case [4] consisted in a male patient, aged 69 years, with DRESS syndrome development 4 weeks after vemurafenib initiation. In both cases, vemurafenib had been prescribed curative for metastatic melanoma. DRESS syndrome is a severe drug reaction whose etiology remains poorly elucidated. The main drugs involved are anticonvulsants and allopurinol. It has recently been shown that certain viruses (HHV-6, EBV, CMV) are involved in the appearance of the reaction [3]. No viral reactivation was observed in the present case. DRESS treatment is mainly based on corticosteroid therapy even though there is currently no validated treatment. A study conducted in 2011 [5] on 38 patients has shown that the complications of DRESS, such as relapse, viral reactivation and septicemia, were less frequent with topical corticosteroids than with systemic corticosteroids. The study therefore concluded that systemic corticosteroid therapy should be restricted to the most serious cases of DRESS. Prospective studies are needed to further elucidate DRESS treatment strategies, and research protocols are being implemented to compare the efficacy of local corticosteroids with systemic corticosteroids. In the present case, given the severity of the presentation, oral corticosteroid therapy was selected and enabled a rapidly positive course. The other 2 cases of vemurafenib-induced DRESS were also treated with systemic corticosteroid therapy (intravenous methylprednisolone followed by a switch to prednisone in the first case, and intravenous prednisolone in the second case) with a positive outcome. Severe drug eruptions on vemurafenib are exceptional. The principal cutaneous toxicity induced by vemurafenib is maculopapular rash, which has been reported in 36–68% of patients and was in the majority of cases of grade ≤3 [3, 5]. The only severe drug eruptions previously reported with vemurafenib, other than the 3 cases of DRESS, consist in 3 cases of toxic epidermal necrolysis [6–8] and 1 case of Stevens-Johnson syndrome [7]. When mild maculopapular rash appears under vemurafenib, vemurafenib continuation with a dosage reduction is recommended (with a reminder with respect to the instructions for photoprotection and nonirritant cutaneous hygiene). In the majority of cases, the toxicity regresses with those measures. It is, however, essential to promote close monitoring with a view to detecting early clinical signs suggesting incipient DRESS. In the 2 cases of vemurafenib-induced DRESS previously reported and in the present case, the signs consisted in facial edema and peripheral lymphadenopathies. Hyperthermia is also an alert sign. The presence of such signs should alert the clinician to the possibility of DRESS, and he should promptly obtain laboratory studies to evaluate supporting biological features of DRESS. Then the decision of whether to stop the drug would be made on a case-by-case basis and dependent on the probability of DRESS per the RegiSCAR criteria. To date, there are no recommendations for the management of
severe drug eruptions on vemurafenib. When the drug eruption has been treated, the question of whether or not to resume vemurafenib therapy arises. In the case of the second patient, a 50% reduction in the dose enabled resolution of the eruption in 10 days. Then, 4 days after resumption of vemurafenib at full dosage, an abrupt onset of DRESS occurred. It therefore appears dangerous to continue vemurafenib in a context suggesting DRESS or to reintroduce vemurafenib after DRESS. Switching to the second BRAF inhibitor authorized for the treatment of metastatic melanoma, dabrafenib [9], may then be considered. To date, no cross-reaction between the 2 therapies has been reported, and no severe drug eruption due to dabrafenib [10, 11] has been observed. However, fewer patients have been treated with dabrafenib than with vemurafenib. In the context of vemurafenib-induced toxic epidermal necrolysis [7], a switch to dabrafenib has been conducted without recurrence of the drug-induced cutaneous reaction.

Conclusion

This case highlights the importance of the awareness of the potential risk of DRESS appearance with vemurafenib even though the frequency of that syndrome is extremely rare compared to that of nonsevere maculopapular rash. An additional difficulty is that DRESS often begins as a diffuse morbilliform/maculopapular eruption. It is therefore necessary to be vigilant in a subject developing maculopapular rash under vemurafenib, to monitor the patient carefully and to seek more specific clinical signs of DRESS such as facial edema, appearance of pustules, hyperthermia and lymphadenopathy. Laboratory tests should also be performed to assess supporting biological features of DRESS. The development of a DRESS syndrome, unlike the single maculopapular rash, necessitates immediate and definitive discontinuation of vemurafenib. Switching from vemurafenib to dabrafenib then appears to be an interesting therapeutic alternative since the efficacy of dabrafenib is the same with less cutaneous adverse reactions.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflicts of interest.

References