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Drug reaction with eosinophilia and systemic symptoms syndrome induced by combination of vemurafenib and cobimetinib in melanoma: A series of 11 cases

To the Editor: The combination of B-Raf and mitogen-activated protein kinase kinase (MEK) inhibitors has become the standard of care in metastatic melanomas harboring the $BRAF^{V600E}$ mutation. Four cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been previously reported in patients treated with vemurafenib alone[1]; 2 of these cases were treated safely with the dabrafenib.[2]

We report 11 cases of DRESS syndrome induced by vemurafenib and cobimetinib identified in Nantes University Hospital Dermatology Department during July 2015-July 2017. Clinical, biologic, and histologic features of these 11 cases are summarized in Table I. The RegiSCAR score[3] was used to diagnose DRESS syndrome (Table II): 6 cases were definite and 5 were probable DRESS syndrome.

Unusual characteristics were observed in the current series. Mainly, an early onset was found in all our 11 cases: 7-11 days after treatment initiation. A delayed onset of symptoms, ie, 2-6 weeks after the first drug intake is usually described in publications on DRESS syndrome. All patients experienced cheilitis, and 6 of them had buccal erosions or pharynx erythema. For all the cases, symptoms lasted >2 weeks, and the mean time to full recovery with no sequelae was 1 month. None of the patients had a fatal evolution. We observed an unusual Sweet syndrome–like histopathologic pattern in 7 out of the 11 patients that included no epidermal alteration but papillary dermal edema and nuclear dust without vascular necrosis and a superficial perivascular lymphocytic dermatitis.

Skin patch tests with vemurafenib and cobimetinib were performed in 3 patients and results were all negative. Interestingly, initiating a combination of other B-Raf and MEK inhibitors, dabrafenib and trametinib, in 7 cases was associated with no recurrence of symptoms. The 4 other patients did not wish to start another B-Raf + MEK inhibitor treatment.

Regarding the pathogenesis, an Epstein-Barr virus (EBV) reactivation was observed in 7 out of the 11 cases, with positive EBV PCR results. In 1 case, it was associated with a positive parvovirus B19 PCR result. All patients who were previously treated with immunotherapy showed EBV reactivation (5 patients). A recent publication has shown an association between a previous treatment with anti-PD1 and the severity of vemurafenib-induced skin disorders, including hypersensitivity syndrome.[4] Finally, 5 patients carried the human leukocyte antigen B44 allele. A recent publication has shown an association between certain human leukocyte antigen alleles and severe cutaneous reactions, but B44 has not been described in association with DRESS syndrome.[4]

We did not identify predictive factors of this drug-induced toxicity. Because the rash always appeared with the combined use of vemurafenib and cobimetinib, determining whether the reaction is more related to the use of 1 of these 2 drugs or the combination is not possible. In our department, in the previous 2 years, vemurafenib cobimetinib combination treatment was initiated in 68 patients and 11 cases of DRESS syndrome occurred, corresponding to 16% of patients treated.

This series demonstrates that DRESS syndrome induced by the vemurafenib and cobimetinib combination treatment is frequent. The early onset of symptoms must not misguide the diagnosis, and treatment should be rapidly discontinued. Dabrafenib and trametinib were safely initiated without recurrence of symptoms.

Table I. Clinical and biological characteristics of 11 patients who experienced severe drug reaction treated with combination of vemurafenib and cobimetinib

Case	1	2	3	4	5	6	7	8	9	10	11
Age, y	48	44	81	74	80	54	69	79	48	79	34
Sex	M	M	F	F	F	F	F	M	F	F	F
No. previous treatments for metastatic disease	1	0	0	2	0	1	0	1	2	0	0
Prior immunotherapy (time between immunotherapy and targeted therapy initiation)	Yes, nivolumab (5 mon)	No	No	Yes, nivolumab (4 mon)	No	Yes, nivolumab (11 mon)	No	Yes, ipilimumab (18 mon)	Yes, nivolumab (7 mon) and ipilimumab (2 mon) alone	No	No
Usual treatment	Ramipril, prednisolone, paracetamol and codeine	paracetamol	acenocoumarin, levothyroxine, furosemide, enalapril and hemigoxine	Bromazepam, fluindione, flecain, atenolol, paracetamol, calcium and colecalciferol, desloratadine, alendronic acid	prednisolone	levothyroxine	Perindopril, paracetamol, codeine, calcium and colecalciferol	paracetamol, oxycodone, phloroglucinol and esomeprazol	pantoprazole, nomogestrol, levothyroxine, paracetamol	Furosemide, nevibolol, perindopril, cetirizine, nicorandil, ezetimibe and simvastatine, memantine, oxazepam, rivaroxaban	alprazolam
Time to rash onset after treatment initiation, d	7	8	7	9	11	8	7	8	6	10	9
Clinical presentation											
Skin involvement	Confluent maculopapular rash with some purpuric elements, facial edema	Confluent maculopapular rash with some purpuric elements, facial edema	Confluent maculopapular rash with some purpuric elements, facial edema	Confluent maculopapular rash with facial edema, purpuric lesions	Confluent maculopapular rash, facial edema	Confluent maculopapular rash with pustules, detachment and purpuric evolution of lesions, facial edema	Confluent maculopapular rash, facial edema	Confluent maculopapular rash	Confluent maculopapular rash, facial edema	Confluent maculopapular rash with facial edema evolving toward purpuric lesions	Confluent maculopapular rash with some purpuric elements, facial edema
Mucosal involvement	Cheilitis, enanthema	Enanthema, conjunctivitis	Cheilitis, buccal and genital erosions	Enanthema, cheilitis, buccal erosion, conjunctivitis	Enanthema, conjunctivitis, buccal erosions, cheilitis	Cheilitis	None	Erosive cheilitis	Erosive cheilitis, keratitis, enanthema	Genital erosions, conjunctivitis	Enanthema
Maximum fever	40.1°C	39°C	39.8°C	39.4°C	39.2°C	39.6°C	38.9°C	38.8°C	39.2°C	38.8°C	39.8°C
Enlarged lymph nodes	Cervical and inguinal	Axillary	Axillary and inguinal	No	Cervical, axillary, inguinal	No	No	Submandibular	No	No	No
Hematologic abnormalities											
Eosinophilia >1.5 × 10^9 cells/L	No (0.26 × 10^9 cells/L)	Yes (2.31 × 10^9 cells/L)	No (0.64 × 10^9 cells/L)	Yes (1.7 × 10^9 cells/L)	Yes (3.38 × 10^9 cells/L)	No (1.44 × 10^9 cells/L)	No (1.14 × 10^9 cells/L)	Yes (1.58 × 10^9 cells/L)	No (0.42 × 10^9 cells/L)	No (0.49 × 10^9 cells/L)	No (1.01 × 10^9 cells/L)

Continued

Table I. Cont'd

Case	1	2	3	4	5	6	7	8	9	10	11
Atypical lymphocytes	2.5%	4%	1%	2%	1%	No	2%	No	No	2%	No
Systemic involvement	Hepatic cytolysis, acute renal failure, pancreatitis	Hepatic cytolysis, acute renal failure, diarrhea*	Hepatic cytolysis and cholestasis, acute renal failure proteinuria, elevated cardiac enzyme, diarrhea*	Hepatic cytolysis, nephrotic syndrome, elevated cardiac enzyme, diarrhea*	Hepatic cytolysis, acute renal failure, proteinuria, diarrhea*	Hepatic cytolysis and cholestasis, acute renal failure with proteinuria, low platelet count	Acute renal failure, hepatic cytolysis, seizure	Acute renal failure	Hepatic cytolysis, acute renal failure, colitis, macrophage activation syndrome	Hepatic cytolysis, seizure, low platelet count, elevated cardiac enzyme, acute renal failure, diarrhea*	Hepatic cytolysis
Cutaneous histopathologic findings	Congestive dermis, lymphoid inflammatory reaction, karyorrhexis	Polymorphic perivascular infiltrate of dermis with numerous eosinophils, dermal edema, karyorrhexis	Mild lymphoid infiltrate of papillary dermal with perivascular reinforcement, karyorrhexis	Papillary dermal edema with some karyorrhexis spots, polymorphic infiltrate with eosinophils	Polymorphic perivascular infiltrate of dermis with dermal edema, karyorrhexis	Spongiotic pattern with polymorphic perivascular infiltrate of dermis, dermal edema, karyorrhexis	Not contributive	Edematous papillary dermis with lymphoid infiltrate	Polymorphic perivascular infiltrate of dermis with high eosinophil count	Not done	Perivascular infiltrate of superficial and deep dermis with high eosinophil count, dermal edema, karyorrhexis
Virus positive for by PCR, blood culture, AAN	EBV, +2.7 log, -	-	EBV, +3.1 log, -	EBV, +2.5 log, -	-	EBV, +4 log and parvovirus B9, +4 log, -	-	EBV, +3.7 log, -	EBV, +3.1 log, -	-	EBV, +2.6 log, -
HLA profile	A02/A23, B44/B51	A23/A29, B44	A03/A32, B07/B44	A2/A11, B35/B63	A01/A02, B08/B27	A24/A29, B13/B27	A26/A31, B44/B45	Not done	A01/A11, B07/B08	A24/A29, B40/B44	A02/A24-B44

AAN, Antinuclear antibody; *EBV*, Epstein-Barr virus; *HLA*, human leukocyte antigen.
*Diarrhea is a common adverse event with vemurafenib and cobimetinib combination drug treatment.

Table II. Clinical and biologic criteria of DRESS syndrome according to RegiSCAR score in the 11 cases reported

Item	Case no.										
	1	2	3	4	5	6	7	8	9	10	11
Fever ≥38.5°C*	0	0	0	0	0	0	0	0	0	0	0
Enlarged lymph nodes (≥2 sites, >1 cm)†	1	0	1	0	1	0	0	0	0	0	0
Atypical lymphocytes†	1	1	1	1	1	0	1	0	0	1	0
Eosinophil concentration‡	0	2	0	2	2	1	1	2	0	0	1
Skin rash§											
Extent >50% of BSA	1	1	1	1	1	1	1	1	1	1	1
≥2 edemas, infiltration, purpura, scaling	1	1	1	1	1	1	1	1	1	1	1
Biopsy suggestive of DRESS*	−1	0	0	0	0	0	−1	0	0	−1	0
Internal organ involved‖	2	1	2	2	2	2	1	0	2	2	1
Resolution >15 days¶	0	0	0	0	0	0	0	0	0	0	0
≥3 biologic investigations performed and negative to rule out alternative diagnoses (ANA; blood culture; HAV, HBV, HCV, chlamydia, and mycoplasma serology)†	1	1	1	1	1	1	1	1	1	1	1
Final score#	6	7	7	8	9	6	5	5	5	5	5

BSA, Body surface area; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *HAV*, hepatitis A virus, *HBV*, hepatitis B virus, *HCV*, hepatitis C virus.
*Score: yes = 0, no = −1.
†Score: yes = 1, no = 0.
‡Eosinophil concentration (score): ≥1500 (2 points), 700-1499 (1 point), and <700 (0 points).
§Score: yes = 1, unknown = 0, no = −1.
‖After exclusion of other explanations: 0 organs (0 points), 1 organ (1 point), and ≥2 organs (2 points).
¶Score: yes = 1, no or unknown = −1.
#Final score: 0-1 = not a case, 2-3 = possible case, 4-5 = probable case, and >5 = definite case.

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Preoperative hypertension increases intraoperative bleeding in patients undergoing Mohs micrographic surgery

To the Editor: Complications after Mohs micrographic surgery (MMS) often involve difficulties with hemostasis.[1,2] An association between systolic blood pressure (BP) and bleeding complications has been reported by others.[3-5] We investigated the role of BP in bleeding outcomes in patients who are undergoing MMS.

BP measurements were recorded in 209 patients (120 men and 89 women who were a median of 73 years of age [interquartile range {IQR} 63-79 years]) who were undergoing MMS for head and neck cancer using a Welch Allyn sphygmomanometer without the surgeon being aware of the result until the procedure was complete.

BP was measured before, during, and after the procedure in 92 patients. In the subsequent 117 patients, only preoperative BP measurements were recorded. The surgeon subjectively graded intraoperative bleeding as mild (no abnormal bleeding), moderate (bleeding increased but controllable), or severe (bleeding very difficult to control) before the BP result was seen. A postoperative review was conducted after 7 days or sooner if required. Hypertension was defined as systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg. Twenty-one patients (10%) were taking an anticoagulant; 47 (22%) patients were taking a platelet inhibitor. Two patients were taking both aspirin and an anticoagulant.

Serial measurements showed that BP was highest preoperatively and fell slightly during the procedure. In all 209 patients, preoperative BP ranged from 104/54 mm Hg to 191/112 mm Hg (mean 145/81 mm Hg). Intraoperative bleeding (Fig 1) was graded as mild in

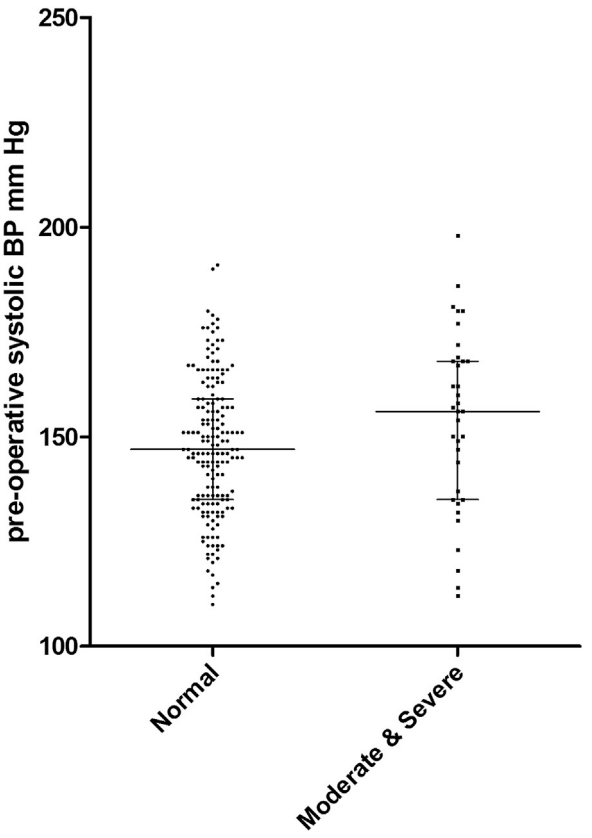

Fig 1. Preoperative systolic blood pressure (BP) and intraoperative bleeding grade. Individual data points shown with median plus or minus interquartile range. The Mann-Whitney U test shows that the 172 patients with normal bleeding (solid diamonds) had a significantly ($P < .05$) lower systolic BP (147 [135-159] mm Hg) than the 35 patients with moderate and severe intraoperative bleeding (solid squares; 156 [135-168] mm Hg).