

Henry Ford Health System

Henry Ford Health System Scholarly Commons

Dermatology Articles

Dermatology

4-6-2017

Development of Papulopustular Rosacea during Nivolumab Therapy for Metastatic Cancer.

Emilie Bousquet

Allison Zarbo

Emilie Tournier

Christine Chevreau

Julien Mazieres

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/dermatology_articles

Authors

Emilie Bousquet, Allison Zarbo, Emilie Tournier, Christine Chevreau, Julien Mazieres, Mario E. Lacouture, and Vincent Sibaud

Development of Papulopustular Rosacea during Nivolumab Therapy for Metastatic Cancer

Emilie BOUSQUET¹, Allison ZARBO², Emilie TOURNIER³, Christine CHEVREAU⁴, Julien MAZIERES¹, Mario E. LACOUTURE⁵ and Vincent SIBAUD^{6*}

¹Pulmonary Medicine Unit, Hôpital Larrey, Centre Hospitalier Universitaire Toulouse, Université de Toulouse III, Toulouse, France, ²Department of Dermatology, Henry Ford Hospital Detroit, Michigan, USA, ³Department of Pathology, Institut Universitaire du Cancer, Toulouse Oncopole, Centre Hospitalier Universitaire de Toulouse, ⁴Department of Medical Oncology, Institut Claudius Regaud, Institut Universitaire du Cancer, Toulouse Oncopole, Toulouse, France, ⁵Dermatology Service, Memorial Sloan Kettering Cancer Center New York, NY, USA, and ⁶Departments of Oncodermatology and Clinical Research, Institut Claudius Regaud, Institut Universitaire du Cancer, Toulouse Oncopole, 1 rue Irene Joliot-Curie, FR-31059 Toulouse cedex, France. *E-mail: sibaud.vincent@iuct-oncopole.fr

Accepted Nov 8, 2016; Epub ahead of print Nov 9, 2016

Dermatological toxicities represent the most frequent immune-related adverse events (irAEs) induced by immune checkpoint inhibitors (1, 2). Safety profiles for anti-CTLA-4 inhibitors (ipilimumab) and agents targeting the programmed cell death (PD-1) receptor (nivolumab, pembrolizumab) appear to be very similar, yet a lower frequency is observed with the latter (2). A non-specific maculopapular rash represents the most frequent cutaneous toxicity of anti-PD-1 inhibitors, with a calculated all-grade incidence of 14.3% and 16.7% for nivolumab and pembrolizumab, respectively (3). These lesions mostly remain mild/moderate, self-limiting, and manageable with topical and/or oral steroids. Other dermatological complications can also occur, including pruritus, xerosis, alopecia, mucosal involvement, autoimmune disorders and vitiligo, the latter being exclusively described in patients treated for melanoma (1–3). More recently, additional skin adverse events have been described, including lichenoid reactions, blistering disorders or occurrence and exacerbation of psoriasis (1–4). We report here 6 patients who developed a mid-facial rash suggestive of papulopustular rosacea, triggered or exacerbated by nivolumab therapy, which has not been reported so far in association with anti-PD-1 therapy.

CASE REPORTS

All patients (5 men, 1 woman) were treated for different types of metastatic solid cancers (**Table I**). Lesions oc-

curred after 1–19 cycles of nivolumab therapy (3 mg/kg every 2 weeks). They were mostly localized on the medial part of the face, with a characteristic combination of papules and pustules on an underlying erythema, consistent with papulopustular rosacea. Symptoms were of mild intensity in all cases (grade 1 papulopustular rash) (**Fig. 1a**) except for one patient, who presented with an intolerable grade 2 toxicity (**Fig. 1b**). Lesions were easily managed with symptomatic treatment (topical metronidazole and/or oral doxycycline), leading to a significant improvement in all cases. Nivolumab therapy was delayed in one patient and resumed after one cycle. Cutaneous biopsy was performed on the patient with grade 2 toxicity, which demonstrated characteristic histopathological features of papulopustular rosacea, with a predominant perivascular and perifollicular CD3⁺ T-cell infiltrate, associated with small and superficial dilated blood vessels. In addition, PD-L1 immunostaining revealed a strong positivity in the perifollicular infiltrate cells (60%) (**Fig. 2**). Close examination of the patients' history suggested pre-existing erythematotelangiectatic rosacea in 3 patients.

DISCUSSION

Development or exacerbation of papulopustular rosacea with anti-PD-1 therapy has not been described previously. We cannot, however, rule out the possibility that this event is under-reported during its development

Table I. Clinical description of reported patients

Case No./ Sex/Age, years	Underlying malignancies	Treatment	Time to onset	Clinical grading ^a	Management	Outcome	Pre-existing rosacea ^b
1/F/48	Melanoma	Nivolumab	19 cycles	Grade 1	Topical metronidazole	Regression	No
2/M/83	Renal cell carcinoma	Nivolumab	1 cycle	Grade 1	Topical metronidazole	Regression	Yes
3/M/68	Tonsillar carcinoma	Nivolumab	4 cycles	Grade 1	Topical metronidazole	Regression	No
4/M/70	Lung cancer	Nivolumab	16 cycles	Grade 2 (intolerable)	Temporary discontinuation, topical metronidazole, oral doxycycline (100 mg/day)	Regression	Yes
5/M/58	Renal cell carcinoma	2 cycles of nivolumab+ipilimumab, followed by nivolumab in monotherapy	8 cycles	Grade 1	Topical metronidazole	Complete resolution ^c	Yes
6/M/66	Melanoma	4 cycles of nivolumab+ipilimumab, followed by nivolumab in monotherapy	15 cycles	Grade 1	Topical metronidazole, oral doxycycline (100 mg/day)	Complete resolution ^c	No

^aFollowing National Cancer Institute CTCAe V4.02. ^berythematotelangiectatic rosacea. ^c4 and 8 weeks after the last dose of nivolumab, respectively.

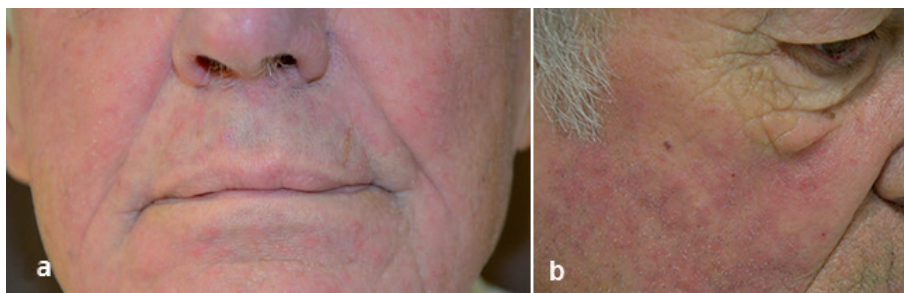


Fig. 1. Clinical examples of nivolumab-induced rosacea. (a) Grade 1 papulopustular rosacea in case 2 and (b) intolerable grade 2 papulopustular rosacea in case 4 induced by nivolumab therapy.

because of unperformed complete skin examination by investigators. Moreover, acneiform rash has been infrequently reported with anti-PD-1 agents, but only by non-dermatologist investigators (5). This so-called “acneiform” rash could potentially correspond, at least in part, to a papulopustular rosacea. The pathophysiology of rosacea remains poorly understood, involving complex dysregulation of the innate immune, vascular and nervous systems (6). However, it has been postulated that the adaptive immune system, involving CD4⁺ Th1/Th17 cell activities, plays a significant role in the development of all subtypes of rosacea (6, 7). In addition, it has been demonstrated that blockade of the PD-1 receptor may promote Th1/Th17 pathways (8). We therefore can speculate that anti-PD-1 monoclonal antibodies may favour the development of either psoriasis (4) or rosacea in predisposed patients. Clinicians should be aware of this new dermatological adverse event, which remains, in our experience, self-limiting, but may lead to temporary

interruption. Early recognition and appropriate management also appear crucial to prevent a negative impact on patients’ quality of life.

ACKNOWLEDGEMENTS

Conflicts of interest: VS has a speaking, consultant or advisory role with Roche, GlaxoSmithKline, Pierre Fabre, Merck, Bristol-Myers Squibb, Bayer and Boehringer Ingelheim. MEL receives research support from Roche/Genentech, Berg, the NIH/NCI Cancer Center Support Grant P20 CA008748; consulting fees from Boehringer Ingelheim, Galderma, Amgen, Roche/Genentech. JM has a speaking, consultant or advisory role with Roche, Bristol-Myers Squibb, PUMA, Pfizer, Novartis, Astra Zeneca and Boehringer Ingelheim. EB, ET, CC and AZ declare no conflicts of interest.

REFERENCES

- Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti PD-1 therapy. *Eur J Cancer* 2016; 60: 190–209.
- 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: 254–263.
- Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016; 60: 12–25.
- Matsumura N, Ohtsuka M, Kikuchi N, Yamamoto T. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. *Acta Derm Venereol* 2016; 96: 259–260.
- Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; 372: 2018–2028.
- Melnik B. Rosacea: the blessing of the celts -An approach to pathogenesis through translational research. *Acta Dermatol Venereol* 2016; 96: 147–156.
- Buhl T, Sulk M, Nowak P, Buddenkotte J, McDonald I, Aubert J, et al. Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways. *J Invest Dermatol* 2015; 135: 2198–2208.
- Dulos J, Carven GJ, van Boxtel SJ, Buddenkotte J, McDonald I, Aubert J, et al. PD-1 blockade augments Th1 and Th17 and suppresses Th2 responses in peripheral blood from patients with prostate and advanced melanoma cancer. *J Immunother* 2012; 35: 169–178.

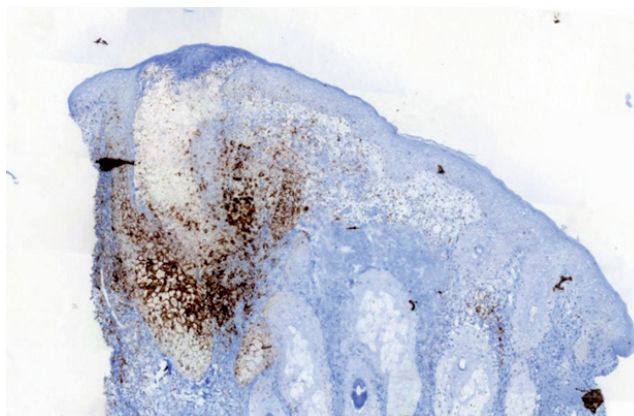


Fig. 2. PD-L1 immunostaining individualizing a strong positivity in the lympho-histiocytic infiltrate, associated with exocytosis into the pilosebaceous follicle (×50 magnification Ventana Ultraview DAB Detection Kit; Antigen retrieval was a standard automated process on the Ventana BenchMark XT clone SP142, Spring Bioscience, Pleasanton, CA, USA).