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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 occurred 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. 1**a) except for one patient, who presented with an intolerable grade 2 toxicity (Fig. 1b). Lesions were easily managed with symptomatic treatment (topical metrodinazole 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

[a]Following National Cancer Institute CTCae V4.02. [b]erythemato-telangiectatic rosacea. [c]4 and 8 weeks after the last dose of nivolumab, respectively.

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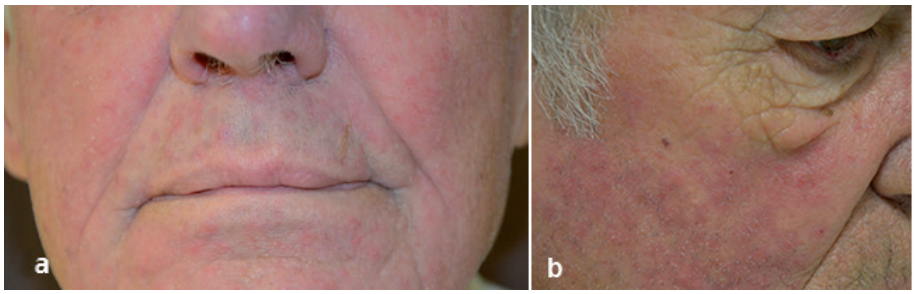

Fig. 1. Clinical examples of nivolumab-induced rosacea. (a) Grade 1 papulopustular rosacea in case 2 and (b) intolerable grade 2 papulopustular rosacea in case 4 induced by nivolumab therapy.

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.

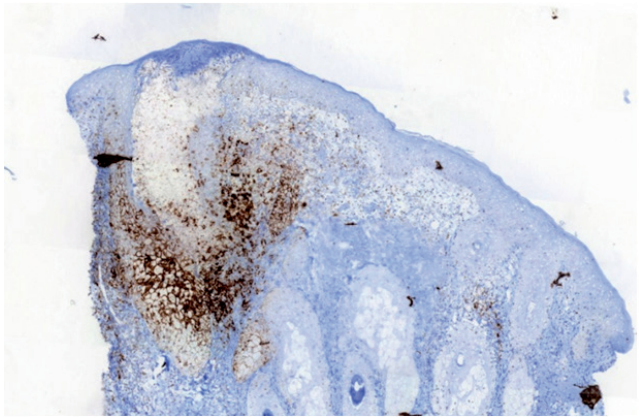

Fig. 2. PD-L1 immunostaining individualizing a strong positivity in the lympho-histiocytic infiltrate, associated with exocytosis into the pilosebaceous follicle (×50 magnification Ventana Ultraview DAB Detection Kit; Antigen retrieval was a standard automated process on the Ventana BenchMark XT clone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

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