Papulopustular rosacea during nivolumab therapy of metastatic squamous cell esophageal carcinoma

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Abstract

We present a 76-year-old man who developed papulopustular rosacea after receiving nivolumab treatment for his esophageal carcinoma, metastatic to the lungs. Nivolumab is an emerging cancer therapy whose immune-related adverse events are still not fully recognized and likely underreported. The treatment has been reported to cause a myriad of cutaneous immune-related adverse events. However, nivolumab-induced-papulopustular rosacea has been scarcely reported. Thus, this case presents a clinically important finding that physicians should be aware of when seeing patients on nivolumab therapy.

Keywords: nivolumab-induced rosacea, papulopustular

Introduction

Papulopustular rosacea is a subtype of rosacea, presenting as papules and/or pustules on the skin of the face in addition to transient or persistent facial redness occurring on the forehead, chin, cheeks, and nose [1]. Papulopustular rosacea can be induced by multiple modalities. Very few cases have reported papulopustular rosacea triggered or exacerbated by nivolumab therapy of metastatic cancer [2]. We present a unique case of a 76-year-old man presenting with papulopustular rosacea induced by nivolumab therapy for treatment of metastatic esophageal carcinoma.

Case Synopsis

A 76-year-old non-smoking man with a past medical history of metastatic esophageal carcinoma cancer requiring a gastrostomy tube, basal cell carcinoma, and squamous cell carcinoma, presented to Pacific Skin Institute with a chief complaint of a red rash on his face present for an unknown duration. The rash was painless and he denied complaints of pruritus or peeling. He endorsed a history of intermittent flushing, papules, and pustules. He denied any prior treatment for the rash. Prior to presentation, he had received two sessions of 240 milligrams of intravenous nivolumab chemotherapy for his metastatic esophageal cancer. In addition, he was on hydrocortisone 2.5 % ointment twice daily as needed for seborrheic dermatitis, topical 5-fluorouracil 5 % to apply to the left hand, and 10 milligrams acitretin by mouth daily along with repeated cryotherapy for numerous actinic keratoses and cutaneous squamous cell carcinomas on the face and upper extremities.

On examination, he had facial erythema and central telangiectasias with numerous papules and pustules without any comedones (**Figure 1**). He received a diagnosis of papulopustular rosacea. He was prescribed topical metronidazole 0.75% cream twice daily along with 50 milligrams/5 milliliter oral doxycycline to take 10 milliliter (100 milligrams) twice daily through his gastrostomy tube. He continued to receive nivolumab per his oncologist and had repeated flares of his rosacea after receiving nivolumab. The patient passed away as a result of his metastatic cancer.

Case Discussion

Nivolumab therapy is a type of targeted immunotherapy used for the treatment of various types of cancers [3]. Specifically, nivolumab is a human immunoglobulin G4 PD1 immune checkpoint inhibitor antibody with anti-tumor effects through its action with the programmed death-1 (PD1) receptor present on activated T cells; PD1 normally functions to decrease immune responses [3]. Tumor cells express PD1L and PD2L receptors which are able to interact with the PD1 receptors to suppress the immune response and continue to proliferate [4]. Nivolumab is able to block the interaction between PD1 and PD1L/PD2L and, as a result, delay tumor growth by inhibiting immune suppression [4]. Nivolumab was first approved for treatment of melanoma and later for metastatic squamous cell esophageal carcinoma [5]. Nivolumab and similar immunotherapies have shown to be very effective. However, they can cause various immune-related adverse events, which are toxicities in the gut, skin, lungs, and more [6].

Although nivolumab is known to cause many side effects including cutaneous reactions, only one case series has presented six patients, described in **Table 1**, with a nivolumab-induced papulopustular rosacea [2]. Since nivolumab is still a relatively new drug, receiving U.S. Food and Drug Administration approval in 2014, many cutaneous side effects may still not be fully known and instances may be underreported [7]. Of cutaneous skin reactions that have been reported, the most common include vitiligo, psoriasis, pruritus, rash, bullous pemphigoid, lichenoid eruption, lupus erythematosus, and erythema multiforme [7–9]. Generally, these reactions have mostly been mild, but some severe cases have been identified [10]. The underlying mechanisms of the cutaneous immune-related adverse events reported and seen in the presenting patient induced by nivolumab are not fully understood. Thus, further research is necessary to understand the cause of such reactions as a rising trend in adverse dermatological events from nivolumab use is being seen.

T cell activation as a result of anti-PD1 therapy most likely has a prominent role in causing the adverse cutaneous reactions [7]. One study suggests that the activated T cells may migrate to the skin where they cause immune-related adverse events [11]. Additionally, studies state that T cells may be identifying antigens on keratinocytes present in the skin that are very similar to the antigens of the target tumor cells and cause an immune attack on the healthy keratinocytes [7,11]. Nevertheless, the cause for our patient to flare with papulopustular rosacea is not clear.

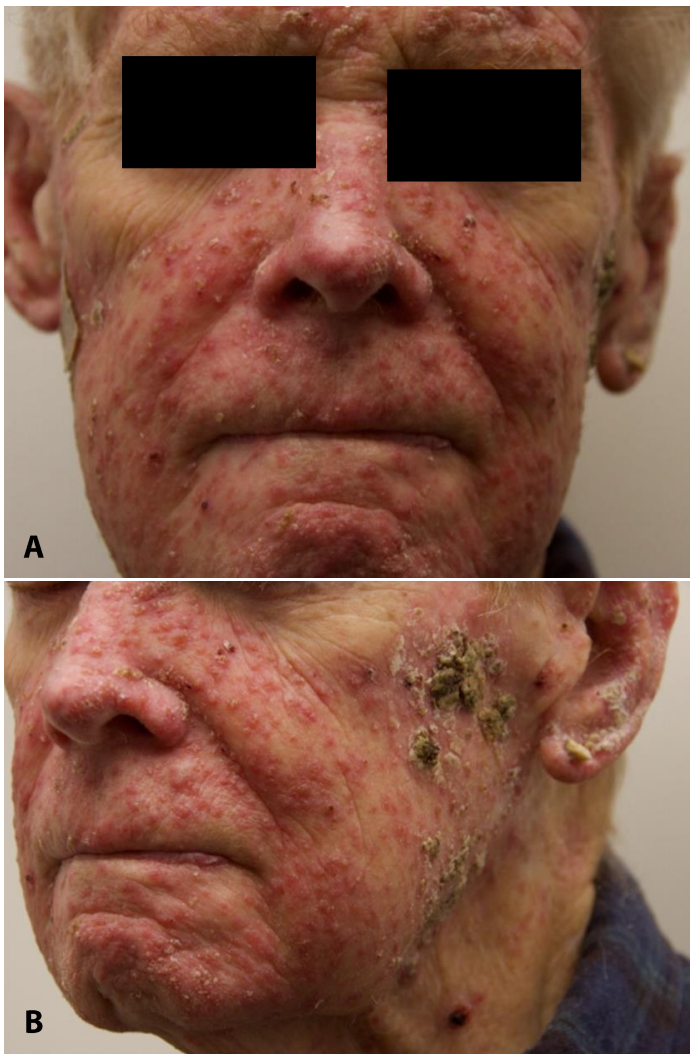

Figure 1. *76-year-old male patient with papulopustular rosacea on the face and multiple actinic keratoses and non-melanoma squamous cell carcinomas.* ***A)*** *Front profile of the face.* ***B)*** *Side profile of the face.*

Conclusion

Nivolumab therapy for cancer has the possibility to cause dermatologic immune-related adverse events in some patients. Herein, we specifically report a case of nivolumab-induced papulopustular rosacea.

Potential conflicts of interest

RKS serves as a scientific advisor for LearnHealth and Arbonne and as a consultant to Burt's Bees, Novozymes, Nutrafol, Abbvie, Leo, Sun -and Regeneron Pharmaceuticals. The remaining authors declare no conflicts of interest.

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Table 1. *Clinical descriptions of reported patients with nivolumab-associated papulopustular rosacea. Cases 1-6 were reported by Bousquet et al. and case 7 describes the presenting patient seen at Pacific Skin Institute [2].*

Case number	Age	Gender	Type of cancer	Nivolumab IV therapy dose	Time of onset of papulopustular rosacea	Treatment prescribed for papulopustular rosacea	Treatment outcome for papulopustular rosacea
1	48	F	Melanoma	3 milligrams/kilogram every 2 weeks	38 weeks	Topical metronidazole prescribed	Regression
2	83	M	Renal cell carcinoma	3 milligrams/kilogram every 2 weeks	2 weeks	Topical metronidazole prescribed	Regression
3	68	M	Tonsillar carcinoma	3 milligrams/kilogram every 2 weeks	8 weeks	Topical metronidazole prescribed	Regression
4	70	M	Lung cancer	3 milligrams/kilogram every 2 weeks	32 weeks	Discontinued nivolumab therapy, topical metronidazole and oral doxycycline (100 milligram/day) was prescribed	Regression
5	58	M	Renal cell carcinoma	3 milligrams/kilogram every 2 weeks	16 weeks	Topical metronidazole prescribed	Complete resolution after 4 weeks of nivolumab therapy completion
6	66	M	Melanoma	3 milligrams/kilogram every 2 weeks	30 weeks	Topical metronidazole and oral doxycycline (100 milligram/day) was prescribed	Complete resolution after 8 weeks of nivolumab therapy completion
7 (presenting patient)	76	M	Metastatic squamous cell esophageal carcinoma	240 milligrams every 2 weeks	4 weeks	Topical metronidazole and 50 milligrams/5 milliliter oral doxycycline to take 10 milliliter (100 milligrams) twice daily through gastronomy tube	No follow up possible due to patient passing away