SKIN

BRIEF ARTICLE

Concomitant Eruptive Squamous Atypia and Bullous Drug Eruption Associated with Pembrolizumab

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ABSTRACT

This study involves the case of a rare eruptive squamous atypia (ESA) reaction and concurrent bullous eruption following pembrolizumab treatment for recurrent neck squamous cell carcinoma. This report aims to raise awareness to possible concurrent skin reactions related to PD-1 inhibitor treatment that has otherwise only been reported twice in melanoma patients.

INTRODUCTION

Pembrolizumab is a programmed cell death protein 1 (PD-1) inhibitor used in the treatment of advanced malignancies including melanoma, lung cancer, and head and neck squamous cell carcinoma (HNSCC). An immune checkpoint inhibitor, pembrolizumab, blocks the attenuation of cellular immunity, thereby promoting immune response activity against malignant cells. Cutaneous reactions are common and range from non-specific eruptions to life-threatening reactions such as Stevens-Johnson syndrome (SJS).[1] Here, we report a case of concomitant development of eruptive squamous atypia (ESA) and a bullous drug eruption in a patient on pembrolizumab.

CASE REPORT

A 77-year-old male presented to dermatology clinic with a diffuse erythematous pruritic and tender rash. The patient had a history of recurrent squamous cell carcinoma (SCC) of the oral cavity treated with partial glossectomy and chemoradiation. About two months prior to presentation, the patient had started pembrolizumab for recurrence of unresectable SCC in the left neck. He began to develop an ill-defined rash involving the legs after the second cycle. On physical exam, he had multiple dome-shaped scaly pink papules and nodules on the legs (**Figure 1**). A biopsy was obtained of one of the nodules (**Figure 2**) and demonstrated a keratoacanthoma-type squamous cell carcinoma, consistent with the initial clinical impression of ESA. He was subsequently started on clobetasol 0.05% ointment under occlusion and further pembrolizumab infusions were held.

At two-month follow-up, the patient reported significant improvement of the nodules on his legs but began to develop new intensely pruritic blisters on his arms, legs, chest, and back. On exam, the patient had pink

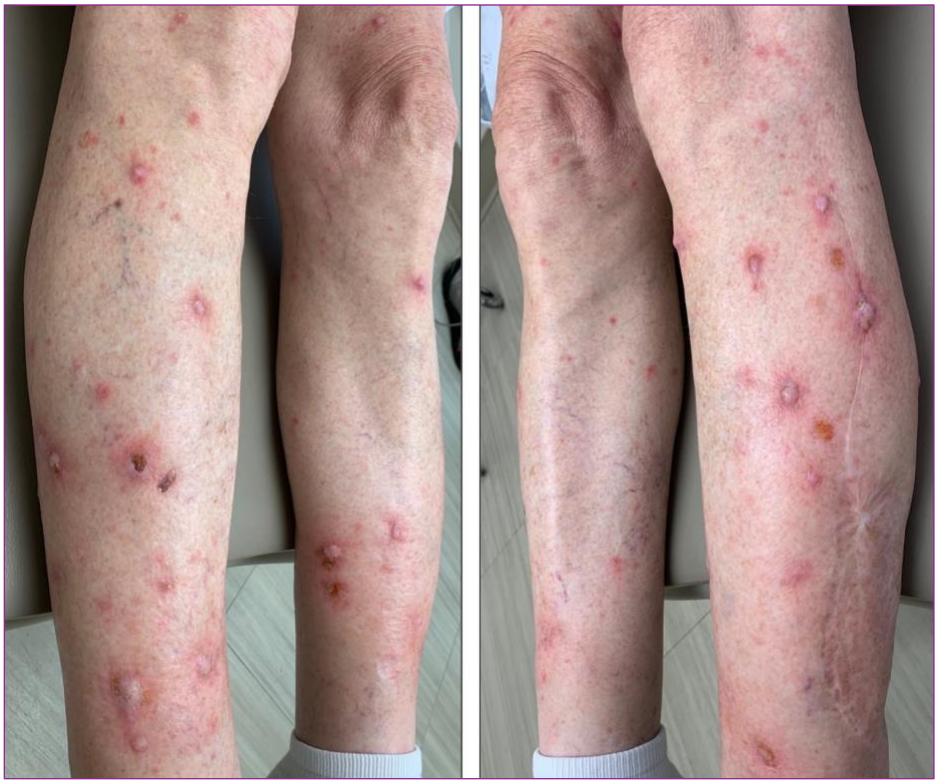

Figure 1. Eruptive Squamous Atypia of the Lower Extremities

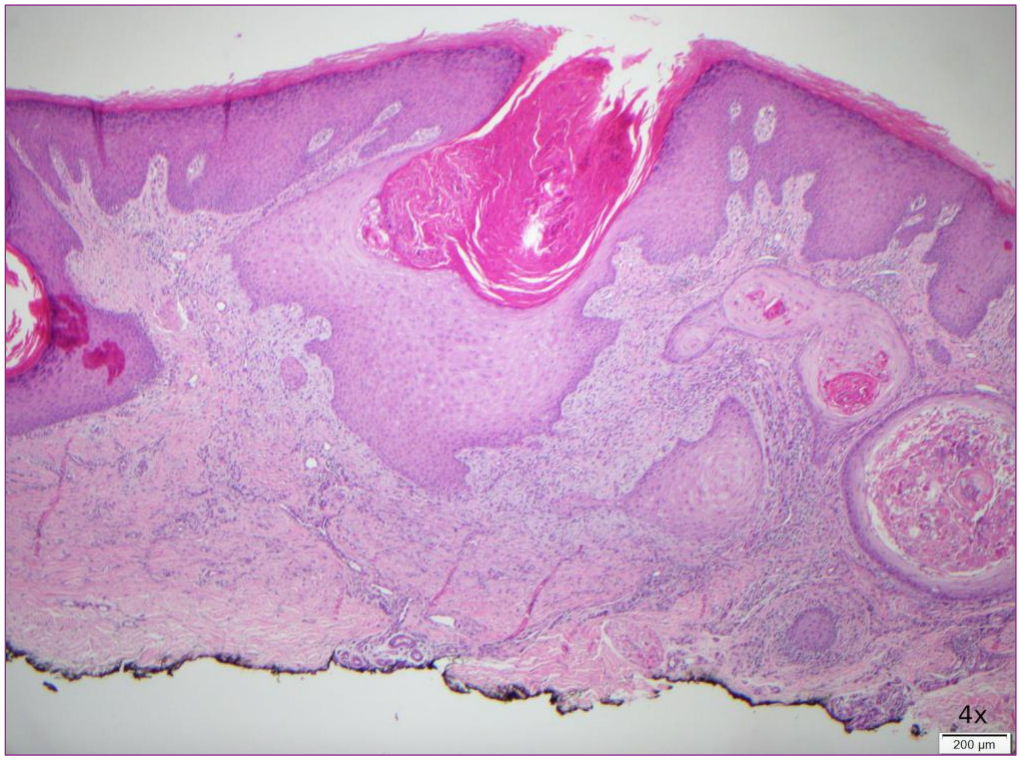

Figure 2. Eruptive Squamous Atypia Pathology Slide.

edematous plaques with some having central round erosions scattered on the chest, back (**Figure 3A**), arms, and legs (**Figure 3B/C**). Another biopsy was performed (**Figure 4A and 4B**) and pathology showed a subepidermal cleft with confluent epidermal necrosis and an inflammatory infiltrate made up of neutrophils, lymphocytes, and occasional eosinophils, in addition to a vacuolar interface dermatitis. Direct immunofluorescence (DIF) was negative. Based on histology, a diagnosis favoring unusual bullous eruption secondary to pembrolizumab was made. The patient was started on a prednisone taper and pembrolizumab was discontinued with the patient opting to follow-up with his local oncologist and dermatologist for further treatment.

DISCUSSION

Immune checkpoint inhibitors have greatly advanced the treatment of many malignancies but are often characterized by immune-related adverse events (irAEs). Cutaneous eruptions can include morbilliform eruption, vitiligo, psoriasis, lichen planus, bullous pemphigoid, and SJS.[1] However, development of cutaneous irAEs is associated with improved response of malignancy to treatment, likely given the immune activation that precipitates these skin manifestations.

Eruptive squamous atypia encompasses an entity more traditionally described as eruptive keratoacanthomas. ESA is characterized by the rapid appearance of multiple hyperkeratotic papules that histologically demonstrates features of low-grade squamous proliferation and may have architecture akin to keratoacanthoma-type squamous cell carcinomas (SCC).[2] Treatment options include topical steroids, topical 5-fluorouracil (5-FU), intralesional 5-FU, cryotherapy, and acitretin with the advantages of these options being good efficacy coupled with avoidance of multiple invasive procedures for removal.[2] Several case reports have identified the association of ESA with pembrolizumab therapy, as well as other PD-1 and PD-L1 inhibitors.[3-7]

Bullous eruptions represent another potential type of cutaneous irAE that may occur. A 2018 single institution retrospective review identified 9 patients with bullous disorders associated with PD-1 and PD-L1 inhibitors.[8] Seven of 9 demonstrated similar histopathological findings to bullous pemphigoid (BP) with 2 of 7 having negative DIF as in our case. Treatment is challenging as involvement of large amounts of body surface area in some cases necessitated cessation of immunotherapy as well as oral steroids or additional immunomodulatory therapy.[8]

Crow et al. hypothesized that ESA development was associated with inflammatory action at the dermal-epidermal junction (DEJ), explaining why there may be an association with lichenoid or bullous eruptions.[5] Our patient had initial presentation of ESA on the lower legs with subsequent progression into bullous lesions on the trunk, upper extremities, and thighs. Otherwise, the development of ESA is seemingly paradoxical with reactive inflammation contributing to epidermal proliferation.[3] Overall, the mechanism underlying development of ESA and bullous disorders secondary to PD-1 inhibitors is poorly understood.

CONCLUSION

The coexisting presentation of ESA and bullous disorder is rare and has been

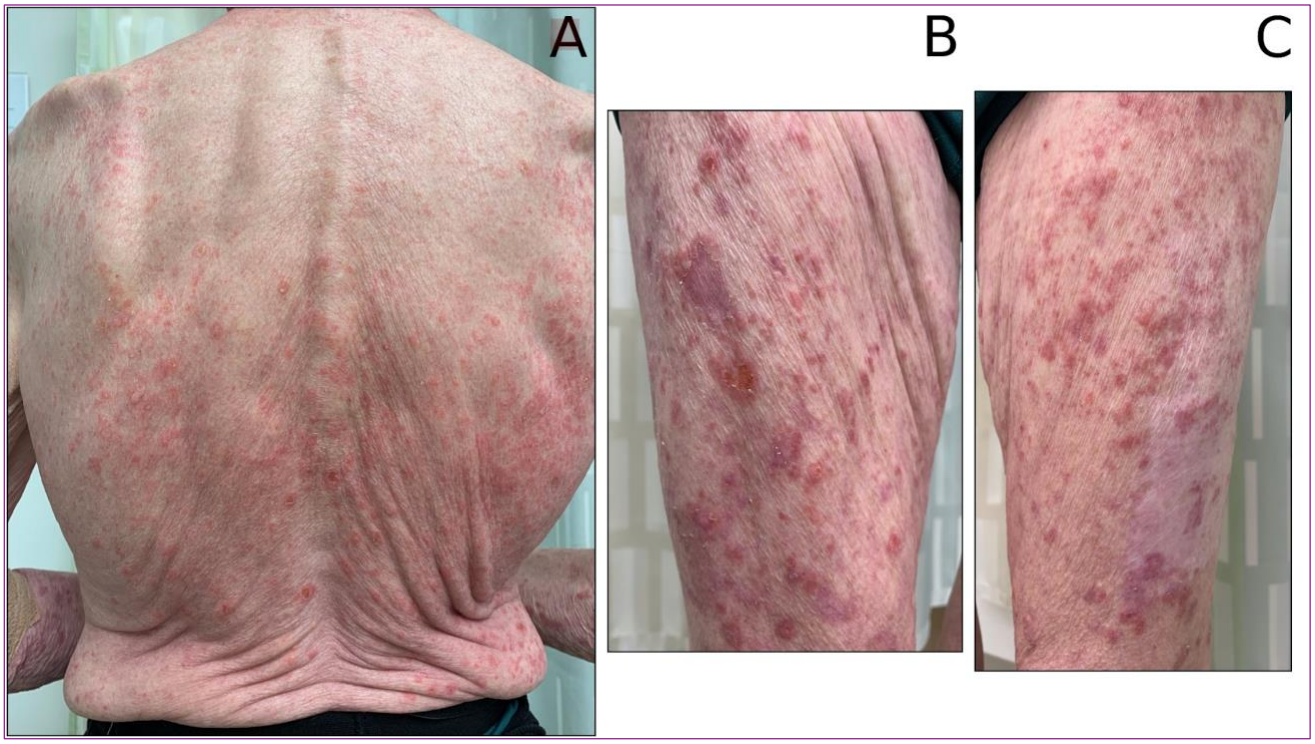

Figure 3. Bullous Drug Eruption of the Back (3A) and Lower Extremities (3B/C)

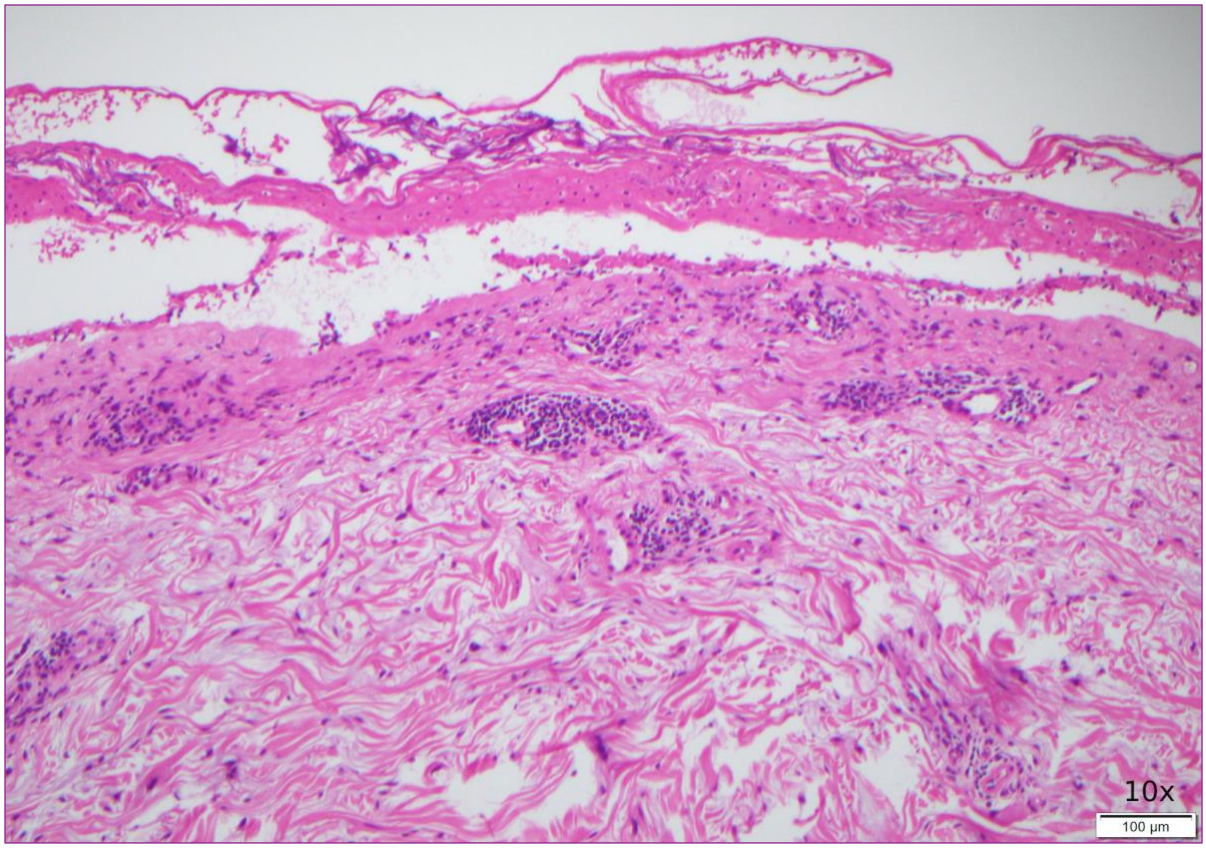

Figure 4. Unusual Bullous Eruption Pathology Slide

reported in just two other cases previously: a patient on pembrolizumab for metastatic melanoma and patient on nivolumab also for metastatic melanoma.[9] In summary, clinicians should be aware of ESA and bullous disorders arising secondary to PD-1 therapy and monitor for distinct morphologies representing overlapping eruptions. Being aware of the possibility of concomitant reaction types can help physicians identify and treat these patients more efficiently.

Conflict of Interest Disclosures: None

Funding: None

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References:

1. Bhardwaj M, Chiu MN , Pilkhwal Sah S. Adverse cutaneous toxicities by PD-1/PD-L1 immune checkpoint inhibitors: pathogenesis, treatment, and surveillance. Cutan Ocul Toxicol 2022;41:73-90.
2. Que SKT, Compton LA , Schmults CD. Eruptive squamous atypia (also known as eruptive keratoacanthoma): Definition of the disease entity and successful management via intralesional 5-fluorouracil. J Am Acad Dermatol 2019;81:111-22.
3. Freites-Martinez A, Kwong BY, Rieger KE, Coit DG, Colevas AD , Lacouture ME. Eruptive Keratoacanthomas Associated With Pembrolizumab Therapy. JAMA Dermatol 2017;153:694-7.
4. Fradet M, Sibaud V, Tournier E, Lamant L, Boulinguez S, Brun A et al. Multiple Keratoacanthoma-like Lesions in a Patient Treated with Pembrolizumab. Acta Derm Venereol 2019;99:1301-2.
5. Crow LD, Perkins I, Twigg AR, Fassett MS, LeBoit PE, Berger TG et al. Treatment of PD-1/PD-L1 Inhibitor-Induced Dermatitis Resolves Concomitant Eruptive Keratoacanthomas. JAMA Dermatol 2020;156:598-600.
6. Chaudhari S, Leon A, Levin E, Neuhaus I , Liao W. Case Report of Multiple Keratoacanthomas and Squamous Cell Carcinomas in a Patient Receiving Pembrolizumab. J Drugs Dermatol 2017;16:513-5.
7. Tembunde Y , Dika MN. Pembrolizumab-Induced Eruptive Keratoacanthomas and Lichen Planus in a Lung Cancer Patient. Cureus 2023;15:e43402.
8. Siegel J, Totonchy M, Damsky W, Berk-Krauss J, Castiglione F, Sznol M et al. Bullous disorders associated with anti–PD-1 and anti–PD-L1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. Journal of the American Academy of Dermatology 2018;79:1081-8.
9. Bandino JP, Perry DM, Clarke CE, Marchell RM , Elston DM. Two cases of anti-programmed cell death 1-associated bullous pemphigoid-like disease and eruptive keratoacanthomas featuring combined histopathology. Journal of the European Academy of Dermatology and Venereology 2017;31:e378-e80.