Debilitating erosive lichenoid interface dermatitis from checkpoint inhibitor therapy

Michael J Davis[1] BMus, Reason Wilken[2] MD, Maxwell A Fung[2,3] MD, Danielle M Tartar[2] MD PhD

Affiliations: [1]Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia, USA, [2]Department of Dermatology, University of California Davis School of Medicine, Sacramento, California, USA, [3]Department of Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, California, USA

Corresponding Author: Danielle M Tartar MD, PhD, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, Email: DTartar@ucdavis.edu

Abstract

As the list of anti-tumor immunotherapy agents and the list of cancers treated by these novel agents grow, a subset of patients experience immune-related adverse events as a result of prolonged stimulation of the immune system. Many different immune related adverse events including colitis, hepatitis, pneumonitis, thyroiditis, hypophysitis, and cutaneous reactions can result from blocking these inhibitory pathways. The full spectrum of cutaneous immune related adverse events secondary to checkpoint inhibitor therapy is still being defined. The reported varied presentations include lichenoid reactions and bullous pemphigoid, amongst others. We present a severe cutaneous reaction, a case of debilitating erosive lichenoid dermatitis. This case emphasizes both the wide range of possible cutaneous reactions and the potential severity of these reactions.

Keywords: checkpoint inhibitor, lichenoid dermatitis, lichenoid toxicity, cutaneous reactions, anti-PD-L1, anti-PD-1, immune related adverse events

Introduction

Anti-cancer immunotherapy with immune checkpoint inhibitors that target programmed cell-death receptor 1 (PD-1) and programmed cell-death ligand 1 (PD-L1) are increasingly used to treat a growing number of cancers including metastatic melanoma, non-small cell lung cancer, Hodgkin lymphoma, renal cell carcinoma, and urothelial carcinoma [1]. These monoclonal antibodies have thus far demonstrated remarkable and durable results by disruption of the PD-1/PD-L1 pathway. PD-1 is expressed on T cells, B cells, monocytes, and natural killer cells, whereas PD-L1 is expressed on antigen presenting cells including macrophages and dendritic cells [2]. Tumor cells can also express PD-L1 as an evasive technique to avoid host immune detection and response [2, 3]. The coupling of PD-1 and PD-L1 results in an inhibitory signal that disrupts T cell activation and function including cytokine production, proliferation, and cytolysis [3]. PD-1 and PD-L1 agents are used to prevent this ligand and receptor coupling, thus removing the resultant inhibition of the immune system and allowing host immune response to tumor cells.

The resultant prolonged immune system stimulation from these inhibitors can also result in a class of side effects called immune related adverse events (irAEs). irAEs can affect different organs and organ systems including the gastrointestinal tract, kidneys, liver, pancreas, eyes, skin, central and peripheral nervous systems, and endocrine system [4]. Reactions can range anywhere from mild to severe and can even be fatal [4]. Management of these irAEs depends on the severity and can include discontinuation of the

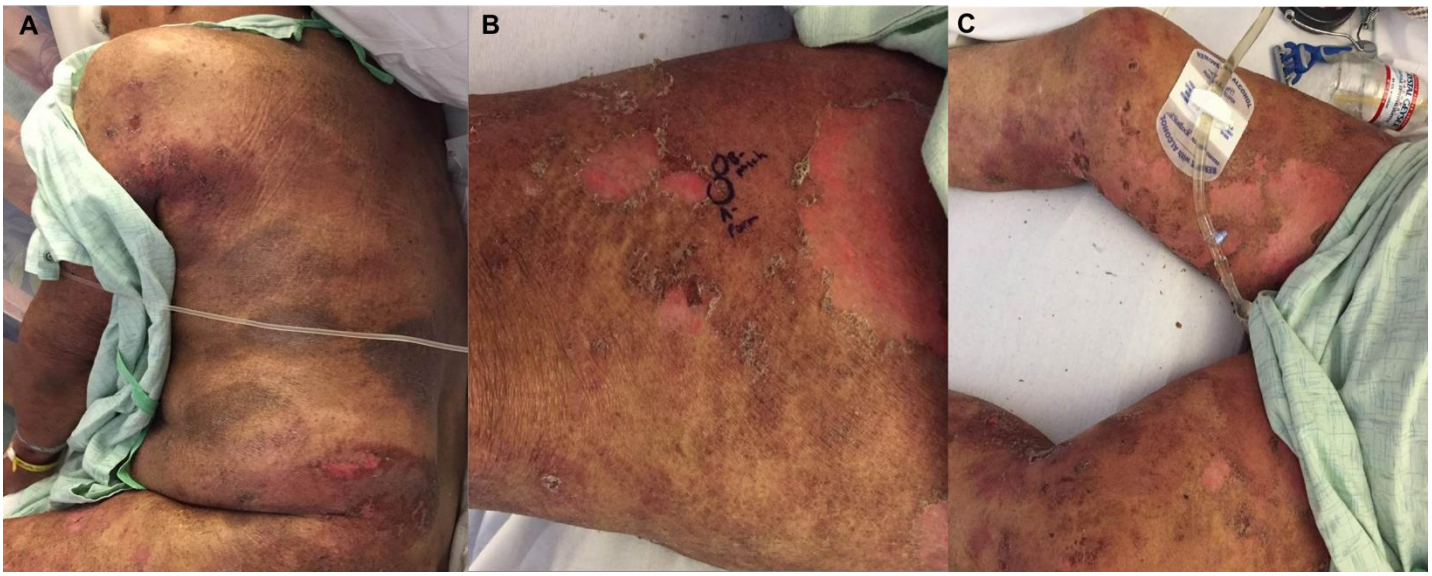

Figure 1. *Severe patchy erythema, crusting, and erosions that developed shortly after the second infusion of atezolizumab, an anti-PD-L1 agent.*

offending agent, long courses of corticosteroids, and anti-tumor necrosis factor therapy [4].

In this manuscript, we present a novel cutaneous reaction to the anti-PD-L1 agent atezolizumab, a case of severe and debilitating erosive lichenoid dermatitis. This case emphasizes both the wide range of possible cutaneous reactions and the potential severity of these reactions.

Case Synopsis

A 71-year-old man with a past medical history significant for type 2 diabetes mellitus, hypertension, chronic kidney disease, transient ischemic attack, and heart failure with preserved ejection fraction was diagnosed with stage 1B adenocarcinoma of the lung. Treatment plan consisted of 6 infusions of atezolizumab every 21 days with concomitant whole body radiation. Approximately 2 weeks after his first infusion of atezolizumab, he experienced generalized pruritus and erythema for which he was prescribed triamcinolone 0.1% cream BID by his primary care provider.

He received his second infusion 1 week later after which he presented to the emergency department with chest pain, productive cough, fevers and chills, and worsening skin eruption. He was empirically started on vancomycin and piperacillin/tazobactam and a dermatology consultation was requested. Physical examination revealed diffuse patchy erythema, crusting, and superficial erosions over the chest, back, and upper and lower extremities without vesicles or bullae and with no involvement of the ocular or intraoral mucosa (**Figure 1**).

Two adjacent biopsies from the left anterior thigh were done, one for hematoxylin and eosin stain and the other for direct immunofluorescence. Histopathologic examination showed a lichenoid lymphohistiocytic infiltrate that obscured the dermal-epidermal junction and that was associated with parakeratosis, basilar squamatization, junctional vacuolar alteration, necrotic keratinocytes, intraepidermal clefting, and scattered eosinophils (**Figure 2**). Direct immunofluorescence (DIF) was negative for epidermal, junctional, or perivascular IgA, IgM, IgG, C3, or fibrinogen. The case presentation in concert with the histopathologic features indicated that this was a lichenoid drug reaction to atezolizumab and the patient was started on prednisone 60mg daily with great improvement in his symptoms, which did not recur after oral prednisone taper. He required transition to an alternative chemotherapy agent.

Discussion

Cutaneous irAEs are relatively common to immunotherapy with anti-PD-1 and anti-PD-L1 agents. A single institutional cohort study by Hwang

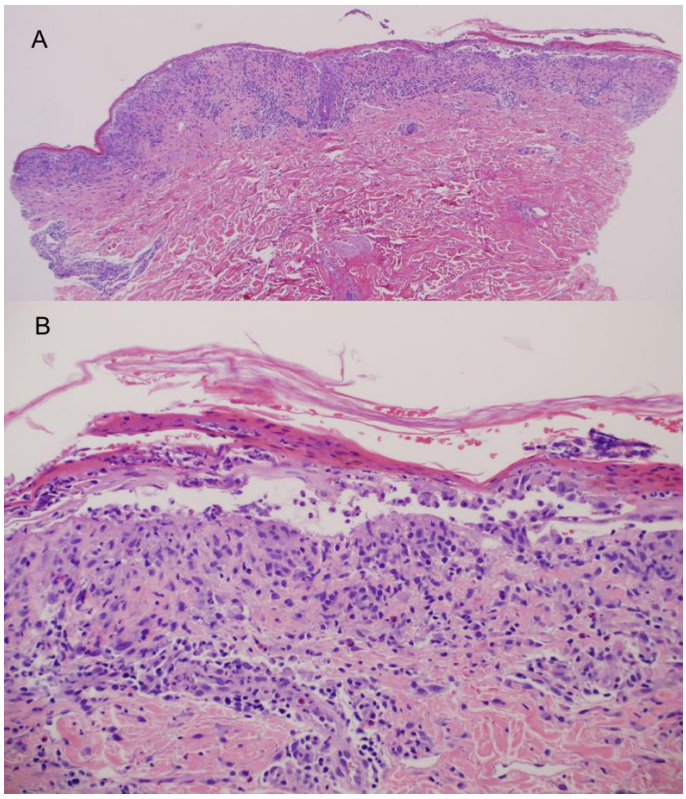

Figure 2. *Lichenoid lymphohistiocytic infiltrate with parakeratosis, necrotic keratinocytes, intraepidermal clefting, and scattered eosinophils blurring the dermal/epidermal junction. H&E, A) 10×, and B) 20×.*

et al. examined 82 patients undergoing PD-1 therapy for metastatic melanoma and found that 49% experienced a cutaneous irAE [5]. The full spectrum of cutaneous irAEs is still being elucidated but includes lichenoid reactions, eczema, vitiligo, bullous pemphigoid, bullous erythema multiforme, psoriasis, toxic epidermal necrolysis, cutaneous sarcoidosis, and eruptive keratoacanthomas [5-8]. Typical reported cases of anti-PD-1 and anti-PD-L1-related lichenoid reactions clinically present as multiple discrete, pruritic, scaly, erythematous, and sometimes violaceous papules and/or plaques [5, 8, 9]. Reported cases of immune checkpoint inhibitor therapy induced bullous pemphigoid presented as tense bullae with linear deposition of C3 and IgG at the basal membrane zone revealed on DIF [6, 10].

In our case, the patient presented with widespread superficial desquamation without bullae in the setting of prolonged immune system stimulation. Biopsy revealed lichenoid lymphohistiocytic infiltrate with junctional vacuolar alteration, necrotic keratinocytes, and scattered eosinophils. These findings were consistent with the histopathology described by Schaberg et al. in their recent manuscript that reported on five cases of lichenoid eruptions associated with anti-PD-1 and anti-PD-L1 therapy [8]. The current case demonstrated intraepidermal clefting, clinically and histopathologically consistent with a more severe erosive expression of interface dermatitis. Erythema multiforme (EM) is also characterized by junctional vacuolar alteration and necrotic keratinocytes and has been documented in association with checkpoint inhibitor therapy. In our case, the clinical presentation was not classically EM-like or lichen planus-like. Histologically, the relatively dense lichenoid pattern favored classification as a lichenoid dermatitis over EM. Based on published reports to date, lichenoid dermatitis appears to be a characteristic and somewhat commonly encountered reaction to checkpoint inhibitor therapy [8, 9, 11-14].

Conclusion

Immunotherapy agents that function as inhibitors along the programmed cell-death 1 axis have proven to be strong additions to the anti-cancer armamentarium. Although these agents are overall well tolerated, the side effect profiles can be significant and can necessitate the cessation of therapy in a subset of patients. It is important that physicians who prescribe PD-1 and PD-L1 therapies to patients and dermatologists who manage these patients are aware of the full spectrum of potential cutaneous irAE that can result from induced stimulation of the immune system. Informed consent for checkpoint inhibitor therapy should include a discussion surrounding the possible cutaneous manifestations and the limits that some of these irAEs will place on continuation of therapy.

References

1. Hirotsu K, Chiou AS, Chiang A, Kim J, Kwong BY, Pugliese S: Localized bullous pemphigoid in a melanoma patient with dual exposure to PD-1 checkpoint inhibition and radiation therapy. *JAAD Case Rep* 2017;3:404-406. [PMID: 28884139].
2. Franklin C, Livingstone E, Roesch A, Schilling B, Schadendorf D: Immunotherapy in melanoma: recent advances and future directions. *Eur J Surg Oncol* 2017;43:604-611. [PMID: 27769635].
3. Mahoney KM, Freeman GJ, McDermott DF: The next immune-checkpoint inhibitors: PD-1/PD-L1 Blockade in Melanoma. *Clin Ther* 2015;37:764-782. [PMID: 25823918].
4. Abdel-Wahab N, Shah M, Suarez-Almazor ME: Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016;11:e0160221. [PMID: 27472273].
5. Hwang SJ, Carlos G, Wakade D, Byth K, Kong BY, Chou S, Carlino MS, Kefford R, Fernandez-Penas P: Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. *J Am Acad Dermatol* 2016;74:455-461.e451. [PMID: 26793994].
6. Kaunitz GJ, Loss M, Rizvi H, Ravi S, Cuda JD, Bleich KB, Esandrio J, Sander I, Le DT, Diaz LA, Brahmer JR, Drake CG, Hollmann TJ, Lacouture ME, Hellmann MD, Lipson EJ, Taube JM: Cutaneous eruptions in patients receiving immune checkpoint blockade: clinicopathologic analysis of the nonlichenoid histologic pattern. *Am J Surg Pathol* 2017;41:1381-1389. [PMID: 28817405].
7. Feldstein SI, Patel F, Larsen L, Kim E, Hwang S, Fung MA: Eruptive keratoacanthomas arising in the setting of lichenoid toxicity after programmed cell death 1 inhibition with nivolumab. *J Eur Acad Dermatol Venereol* 2017. [PMID: 28776778].
8. Tetzlaff MT, Nagarajan P, Chon S, Huen A, Diab A, Omar P, Aung PP, Torres-Cabala CA, Mays SR, Prieto VG, Curry JL: Lichenoid dermatologic toxicity from immune checkpoint blockade therapy: a detailed examination of the clinicopathologic features. *Am J Dermatopathol* 2017;39:121-129. [PMID: 28134729].
9. Schaberg KB, Novoa RA, Wakelee HA, Kim J, Cheung C, Srinivas S, Kwong BY: Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol* 2016;43:339-346. [PMID: 26762844].
10. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, Postow MA, Weinstein A, Lucas AS, Ciccolini KT, Quigley EA, Lesokhin AM, Paik PK, Chaft JE, Segal NH, D'Angelo SP, Dickson MA, Wolchok JD, Lacouture ME: Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res* 2016;4:383-389. [PMID: 26928461].
11. Chou S, Zhao C, Hwang SJE, Fernandez-Penas P: PD-1 inhibitor-associated lichenoid inflammation with incidental suprabasilar acantholysis or vesiculation-report of 4 cases. *J Cutan Pathol* 2017;44:851-856. [PMID: 28753281].
12. Sibaud V, Eid C, Belum VR, Combemale P, Barres B, Lamant L, Mourey L, Gomez-Roca C, Estilo CL, Motzer R, Vigarios E, Lacouture ME: Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings. *J Eur Acad Dermatol Venereol* 2017;31:e464-e469. [PMID: 28519570].
13. Guggina LM, Yanes DA, Choi JN: Inverse lichenoid drug eruption associated with nivolumab. *JAAD Case Rep* 2017;3:7-9. [PMID: 28054020].
14. Chou S, Hwang SJ, Carlos G, Wakade D, Fernandez-Penas P: Histologic assessment of lichenoid dermatitis observed in patients with advanced malignancies on antiprogramed cell death-1 (anti-PD-1) therapy with or without ipilimumab. *Am J Dermatopathol* 2017;39:23-27. [PMID: 28045749]..