Fixed drug eruption from atezolizumab

Donovan Kearns[1], Jeffrey T Gardner II[1], Justin Kerstetter[2], Betsy Furukawa[1]

Affiliations: [1]Department of Dermatology, Loma Linda University, Loma Linda, California, USA, [2]Department of Pathology, Loma Linda University, Loma Linda, California, USA

Corresponding Author: Jeffrey T Gardner II, 25865 Barton Road, Suite 101, Loma Linda, CA 92354, Tel: 909-558-2890, Email: jgardner0346@gmail.com

Abstract

Fixed drug eruption (FDE) is a cutaneous drug reaction that tends to recur in the same area (fixed location) upon re-exposure to the offending agent. We present a 48-year-old woman with FDE being treated for metastatic breast cancer with atezolizumab. We believe this is the first reported case of FDE secondary to atezolizumab.

Keywords: atezolizumab, breast, cancer, fixed drug eruption

Introduction

Fixed drug eruption (FDE) is a cutaneous drug reaction that tends to recur in the same area (fixed location) upon exposure to the offending agent [1]. Acute FDE typically presents with well circumscribed, oval, dusky red or violaceous patches or plaques. Some patients may develop a central vesicle or bulla in the lesion. Lesions may appear anywhere including mucous membranes. The condition is believed to be caused by sensitization of intraepidermal CD8+ T cells to a specific medication [2]. Upon exposure to the drug, memory T cells react to the antigen and release cytokines including IFNγ, triggering a localized inflammatory reaction followed by epidermal injury. Although any drug may elicit an FDE, nonsteroidal anti-inflammatory drugs, acetaminophen, and antibiotics are among the most common causative agents [3].

Case Synopsis

A 48-year-old woman with a history of treatment-refractory breast cancer was referred to the dermatology department with complaints of new-onset pruritic rash. Weeks prior to this eruption, the patient was given one dose each of aspirin, ketorolac, hydrocodone-acetaminophen. In addition, she was given an infusion of paclitaxel and ondansetron and started on a course of amoxicillin-clavulanate for 10 days. Our patient's only home medication was acetaminophen as needed. Days prior to this rash, she was started on a chemotherapy infusion of atezolizumab for the first time, along with paclitaxel, acetaminophen, ondansetron, and diphenhydramine given with her infusion. Physical examination of the patient showed multiple edematous and violaceous patches with a focal eroded center on her arms, back, and legs, bilaterally. Atezolizumab was held during her next infusion cycle to see if it was causing the new rash. The next infusion cycle weeks later (paclitaxel, ondansetron, acetaminophen, diphenhydramine) without atezolizumab was uneventful and the patient developed no new lesions. A third infusion including atezolizumab was given and within 2 hours the patient had recurrence of the lesions at previous sites on her arms and legs, as well as new lesions on her head and back. Physical examination of the patient showed multiple edematous, violaceous plaques with a central vesicle, mixed with older crusted lesions from her previous episode (**Figure 1**). Histology from a punch biopsy of a lesion showed intraepidermal necrotic keratinocytes with patchy spongiosis and eosinophilic predominant inflammation (**Figure 2**). A diagnosis of fixed drug eruption secondary to atezolizumab was made after correlating the biopsy results with the patient's clinical presentation.

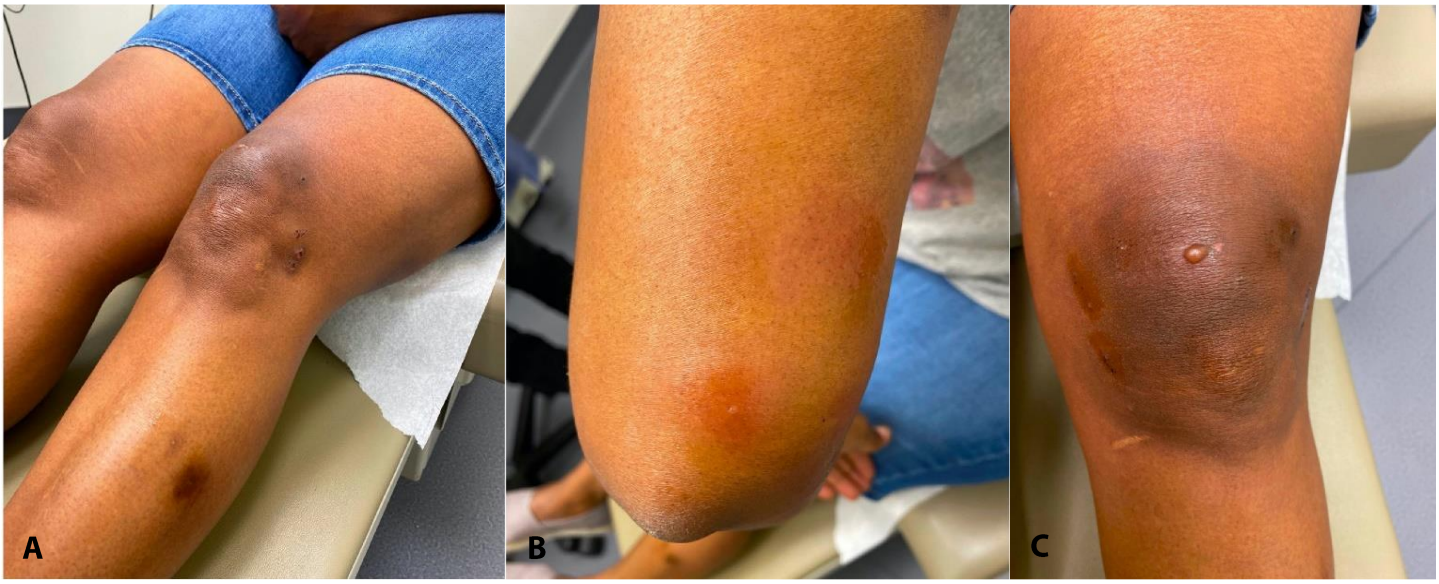

Figure 1. ***A)*** *Bilateral lower extremities after second infusion of atezolizumab.* ***B)*** *Left posterior arm after second infusion of atezolizumab.* ***C)*** *Left knee after second infusion of atezolizumab.*

After treating the patient's lesions with a combination of topical and oral and corticosteroids (short courses of prednisone 20mg daily), a plan was coordinated with her medical oncologist to continue atezolizumab with the use of pre-medication IV methylprednisolone (16mg), diphenhydramine, and famotidine. This regimen greatly reduced the size and severity of lesions that arose with subsequent atezolizumab infusions and the patient has since tolerated its use with her scheduled chemotherapy cycles.

Case Discussion

Atezolizumab is a fully humanized monoclonal antibody used to treat several types of cancer [4], including triple negative breast cancer, metastatic urothelial carcinoma, and non–small-cell lung cancer [5]. The medication is an immune checkpoint inhibitor, which works by specifically targeting PDL1 (programmed cell death ligand 1) and thus blocking the interaction between programmed cell death protein (PD1) and B7 [4]. Blockage of this pathway leads to increased survival of cytotoxic T cells and increased levels of immune surveillance, which helps to decrease tumor burden. The most commonly reported side effects to atezolizumab are fatigue (24.5%), decreased appetite (13.2%), nausea (12.3%), and diarrhea (10.8%). Rash was reported to occur in 8.4% of patients who received the medication, but unfortunately the exact type of eruption was not specified in the data set. Thus, we are not aware of any previous patients developing a fixed drug

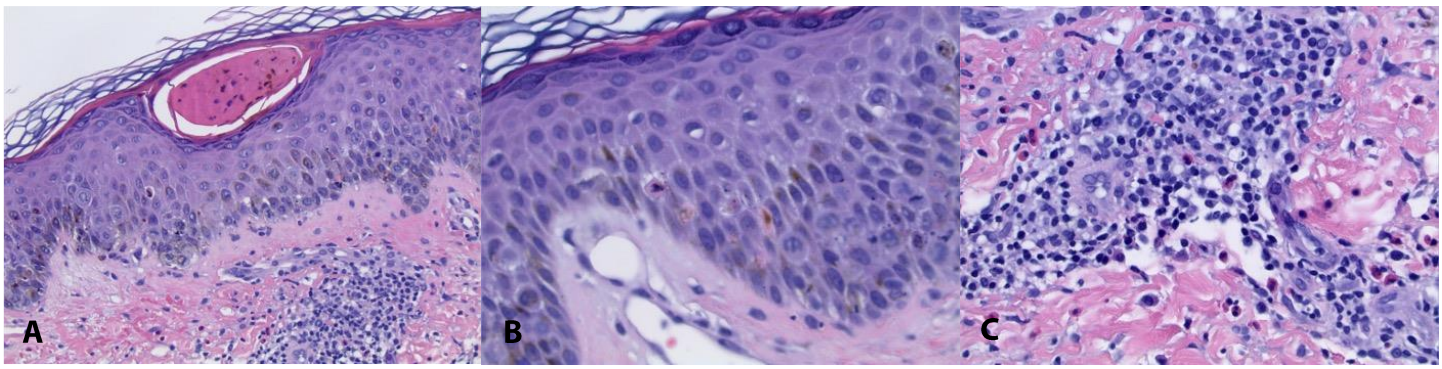

Figure 2. *H&E histopathology.* ***A)*** *Spongiosis and scattered intraepidermal necrosis keratinocytes, 20×;* ***B)*** *scattered intraepidermal necrotic keratinocytes, 40×; and* ***C)*** *perivascular eosinophils, 40×.*

Table 1. *Monoclonal antibodies reported to cause fixed drug eruption (including atezolizumab reported here).*

Drug	Target	Antibody Type	Other reported cutaneous adverse drug reactions
Atezolizumab [7]	PDL1	Humanized	Steven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia systemic symptoms (DRESS), exfoliative dermatitis
Galcanezumab [8]	CGRP ligand	Humanized	Injection site reactions
Adalimumab [9,10]	TNFα	Human	Leukocytoclastic vasculitis, urticaria, eczematous dermatitis and pustular eruptions
Ustekinumab [11]	IL12/IL23	Human	Lymphomatoid drug eruption, erythema annulare centrifugum, bullous pemphigoid, erythema multiforme, eczematous drug eruptions

reaction in response to treatment with this drug. Other PD1 inhibitors have been shown to cause cutaneous side effects (**Table 1**) in as many as 49% of patients receiving them, with 17% developing lichenoid reactions and eczema and 15% developing vitiligo [6]. Due to the drugs' mechanism of action, patients are at increased risk for T-cell mediated diseases. It is possible that atezolizumab may lead to increased risk for T-cell mediated delayed hypersensitivity reactions, including fixed drug eruptions. To our knowledge, this is the first documented case of fixed drug eruption secondary to treatment with atezolizumab.

Conclusion

Fixed drug eruption (FDE) is a cutaneous drug reaction that tends to recur in the same area (fixed location) upon exposure to the offending agent. Atezolizumab is a fully humanized monoclonal antibody used to treat several types of cancer, including triple negative breast cancer. We present a case of FDE to atezolizumab in a patient with metastatic breast cancer.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Valeyrie-Allanore L, Obeid G, Revuz J. Drug Reactions. In: Dermatology. Bolognia J, Jorizzo J, Schaffer J, Cerroni L, editors. 4th ed. Elsevier Limited; 2018, pp. 360.
2. Shiohara T, Mizukawa Y, Teraki Y. Pathophysiology of fixed drug eruption: the role of skin-resident T cells. *Curr Opin Allergy Clin Immunol.* 2002;2:317-23. [PMID: 12130946].
3. Jung JW, Cho SH, Kim KH, Min KU, Kang HR. Clinical features of fixed drug eruption at a tertiary hospital in Korea. *Allergy Asthma Immunol Res.* 2014;6:415-20. [PMID: 25228998].
4. Tie Y, Yang H, Zhao R, et al. Safety and efficacy of atezolizumab in the treatment of cancers: a systematic review and pooled-analysis. *Drug Des Devel Ther.* 2019;13:523-38. [PMID: 30787594].
5. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med.* 2018;379:2108-21. [PMID: 30345906].
6. Hwang SJ, Carlos G, Wakade D, et al. 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;74:455-61 e1. [PMID: 26793994].
7. Collins LK, Chapman MS, Carter J, et al. "Cutaneous adverse effects of the immune checkpoint inhibitors." *Curr Probl Cancer.* 2017;41:125-128. [PMID: 28190531].
8. Klager S, Khalil M, Shulman K, et al. "Galcanezumab-induced fixed drug eruption." *JAAD Case Rep.* 2021;9:90-92. [PMID: 33665287].
9. 9.Bhadresha S, Hughes AJ, McMahon L, et al."Fixed drug eruption secondary to adalimumab." *Clin Exp Dermatol.* 2021;46:366-368. [PMID: 33448464].
10. Li PH, Watts TJ, Chung HY, Lau CS. Fixed Drug Eruption to Biologics and Role of Lesional Patch Testing. *J Allergy Clin Immunol Pract.* 2019;7:2398-2399. [PMID: 31326380].
11. Hafez DM, Alshehri N, Alshehri H, et al. "Ustekinumab-induced fixed drug eruption." *JAAD Case Rep.* 2020;6:1234-1235. [PMID: 33294551].