SKIN

BRIEF ARTICLE

A Novel Case of Eruptive Keratoacanthomas Associated with Apalutamide Treatment for Prostate Cancer

Natasha Baah, DO[1], George Skandamis, MD[2]

[1] Department of Family Medicine, Holzer Health System, Gallipolis, OH
[2] Universal Dermatology & Vein Care, Columbus, OH

ABSTRACT

Recently, there have been cases reporting generalized eruptive keratoacanthomas (EKA) in association with use of the program cell death (PD-1) targeting drugs like nivolumab, pembrolizumab, and leflunomide when treating malignancy. However, based on our literature review, we were unable to find documented cases involving apalutamide. We present the case of an 86-year-old Caucasian male with castration-resistant prostate cancer following radical prostatectomy diagnosed with biopsy-confirmed EKA with squamous cell carcinoma (SCC) two and a half months after the initiation of apalutamide.

INTRODUCTION

Prostate cancer is the second most common cancer globally diagnosed in men[1], with more than 160,000 new cases each year in the United States.[2] Even with relatively high rates of survival, many deaths occur due to metastases. It most often metastasizes to bone, to other sites including lymph nodes, lungs, and liver as well.[1,3] A wide range of treatment options are currently available — active surveillance, surgery, radiation, chemotherapy, and hormonal therapeutics.[2] Although most patients experience remission with standard therapy, approximately 10-20% of prostate cancer cases are castration-resistant.[4] Up to 16% of these patients show no evidence that the cancer has spread at the time of the castration-resistant diagnosis.[4] Castration-resistance refers to continued tumor growth despite appropriate hormonal treatment. In February 2018, apalutamide, a nonsteroidal antiandrogen (NSAA), was approved by the Food and Drug Administration (FDA) as the first drug for non-metastatic castration-resistant prostate cancer.[4]

Recently, there have been cases reporting generalized eruptive keratoacanthomas (EKA) in association with use of the program cell death (PD-1) targeting drugs like nivolumab, pembrolizumab, and leflunomide when treating malignancy. [5,6,7] However, based on our literature review, we were unable to find documented cases involving apalutamide.

We present the case of an 86-year-old Caucasian male with castration-resistant prostate cancer following radical prostatectomy diagnosed with biopsy-confirmed EKA with squamous cell carcinoma (SCC) two and a half months after the initiation of apalutamide.

CASE REPORT

The patient is an 86-year-old Caucasian male who presented with skin lesions that were rapidly enlarging, dome-shaped nodules with central hyperkeratotic depressed cores that resembled volcanos located on the left forearm and bilateral lower extremities (Figure 1A, 1B). Patient stated that the lesions had been there for two and a half months and that he had not received any treatment for them. He has no family history of non-melanoma skin cancer or melanoma.

Past medical history is significant for squamous cell skin cancer on the left central forehead and prostate cancer, for which he underwent a radical prostatectomy 25 years ago. The patient indicated that he was never told the stage of his prostate cancer. He remained symptom free until 2013 when a yearly physical indicated subsequent rising prostate specific antigen (PSA) levels. The patient was placed on leuprolide acetate for two years. PSA levels showed a promising decrease but were not satisfactory given patient history of prostatectomy.

In April 2018, the patient was transitioned to apalutamide 240 mg (four 60mg tablets). One month later, the patient began experiencing a mild, but non-bothersome, pruritus sensation bilaterally on his legs, followed by a slowly developing rash that was not initially biopsied During month three, the same lesions dramatically erupted on both his arms and legs with greater intensity described as moderate and bothersome. Simultaneously, the patient was informed that his PSA levels were starting to rise once again. By month four, apalutamide was discontinued, and the patient was referred to dermatology for evaluation of the eruptive rash, that had decreased in intensity. It is worth noting that trauma from the various levels of the itch-scratch cycle could have played a role in precipitating his lesions. Although based on how the patient recollected the events, we do not believe that the trauma inflicted would have been significant enough to cause the presenting rash. Reports in the literature have described apalutamide-related dermatological adverse events consisting of maculopapular rashes (33.8%) and xerosis (32.4%) [11], toxic epidermal necrolysis (TEN), and psoriatic skin lesions, lichenoid drug eruptions, and urticaria.[12]

In August 2018, the patient presented to dermatology for the initial consultation (Figure 1A, 1B). The given clinical history made a drug reaction highly probable for causing the presenting rash. Shave biopsies showed well-differentiated squamous cell carcinoma with keratoacanthoma-type features. The left proximal pre-tibial region, left distal calf, and left distal dorsal forearm lesions showed crateriform invagination of the epidermis containing atypical squamous cells with eosinophilic cytoplasm. The right and left distal calves and right proximal dorsal forearm showed dermal lobules of mildly atypical squamous cells with identifiable intercellular bridges and areas of keratinization. The treatment regimen consisted of the discontinuation of apalutamide; triamcinolone acetonide 0.1% topical steroid cream to be applied twice daily on affected areas to reduce the swelling, itching, and redness; and topical calcipotriene cream (for the plaque-like lesions) combined with 5-fluorouracil cream (for the acanthosis) applied once daily for seven to ten days. Mohs surgery was utilized for the removal of the tumor lesions over the next several months. By October, the lesions showed significant improvement from initial presentation (Figure 2). We did not consider restarting apalutamide due to limited knowledge on the pathogenesis and patient dissatisfaction with alternatives as documented in recent studies.

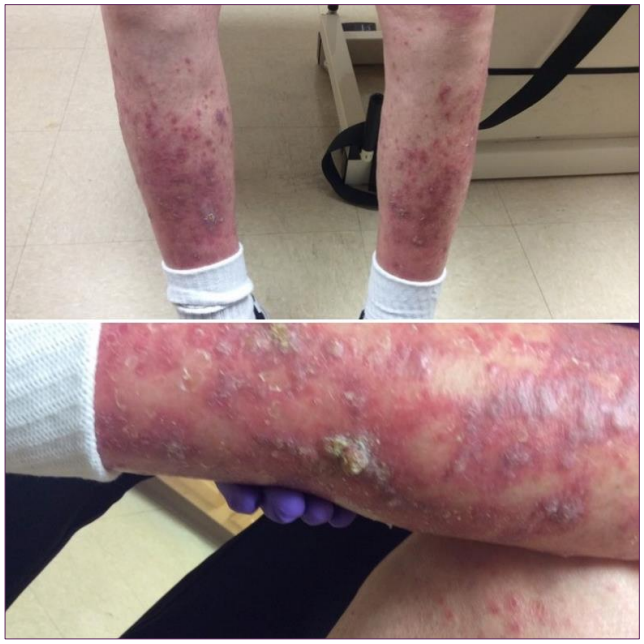

Figure 1. Initial consultation, three months after the initiation of apalutamide – August 2018

DISCUSSION

Apalutamide is an NSAA approved for the treatment of non-metastatic castration-resistant prostate cancer since 2018.[3] Apalutamide induces a therapeutic effect through the competitive antagonism of the androgen receptor at the androgen binding site. Cell growth gene transcription is inhibited through inactivation of the receptor causing prostatic cells to undergo apoptosis leading to effectiveness in refractory prostate cancers.[3] The patient presented with initial eruptive keratoacanthomas one month after the addition of apalutamide 240 mg daily with subsequent full onset of the lesions by month two.

Keratoacanthomas (KA) are rapidly growing, self-resolving, atypical squamous cell proliferations that can be considered a low-grade squamous cell carcinoma (SCC).[6,8] Because distinguishing KAs from invasive SCC can be difficult, they are often treated as if they are malignant neoplasms. [8] KA lesions appear in solitude secondary to an array of causes or multiple may arise in a generalized distribution as a manifestation of a syndrome.[2,3] Eruptive KA (EKA) lesions are distinguished from those associated with syndromes by rapid onset and decreased duration of EKA lesion presence.

EKA is a rare variant of multiple KAs affecting the skin and mucous membranes first described in 1950 as the relative sudden onset of severely pruritic, numerous small flesh-colored follicular papules 1-3 mm in diameter, with central keratin centers, papillomatosis, acanthosis, and glassy eosinophilic hyaline keratinocytes.[9,10] Although there is a well-established correlation with immunosuppression and squamous cell carcinoma, a link has not been determined between immunosuppression and eruptive keratoacanthomas.

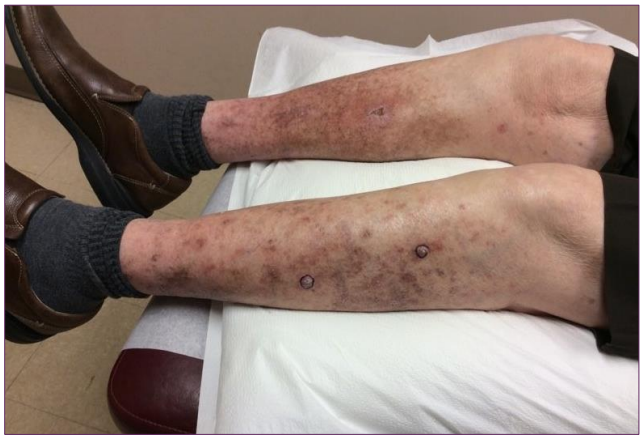

Figure 2. Follow up with treatment regimen topical triamcinolone acetonide 0.1% cream, topical calcipotriene cream combined with 5-fluorouracil, and Mohs surgery - October 2018.

CONCLUSION

The patient described had previous medical history of squamous cell carcinoma, which could increase his predisposition to developing EKA. In patients treated with immunomodulators previously described, the

eruptive keratoacanthomas resolved with the discontinuation of the medication and systemic retinoids. However, treatment of eruptive keratoacanthomas is not limited to retinoids and may include surgical removal, cyclophosphamide[10], or intralesional corticosteroids. The patient in this case showed successful treatment with combination therapy of triamcinolone acetonide 0.1% and calcipotriene combined with 5-fluorouracil cream. The mechanism of apalutamide-induced eruptive keratoacanthomas has yet to be elicited but shows a potential correlation evident in this patient.

Abbreviation and Acronym List

EKA = eruptive keratoacanthomas

FDA = Food and Drug Administration

KA = keratoacanthomas

NSAA = nonsteroidal antiandrogen

PD-1 = program cell death

PSA = prostate specific antigen

SCC = squamous cell carcinoma

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
George Skandamis, MD, FAAD
Universal Dermatology & Vein Care
425 Metro Place North
Suite 195
Dublin, OH 43017
Office phone: (614)706-3057
Email: gskandamis@gmail.com

References:

1. Merriel SW, Funston G, & Hamilton W. Prostate cancer in primary care. *Adv Ther*. 2018; 35(9): 1285–1294. doi: 10.1007/s12325-018-0766-1.
2. Litwin MS & Tan HJ. The diagnosis and treatment of prostate cancer: a review. *JAMA*. 2017; 317(24):2532-2542. doi:10.1001/jama.2017.7248.
3. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Grff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, Lopez-Gitliz A, & Trudel GC. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018; 378(15):1408-1418. doi: 10.1056/NEJMoa1715546.
4. FDA Updates. New non-metastatic, castration-resistant prostate cancer treatment. *Onc Times.* 2018; 40(6):17. doi: 10.1097/01.COT.0000531953.43104.c7.
5. Bednarek R, Marks K, Lin G. Eruptive keratoacanthomas secondary to nivolumab immunotherapy. *Int J Dermatol*. 2018; 57(3):e28-e29. doi: 10.1111/ijd.13893.
6. Freites-Martinez A, Kwong BY, Rieger KE, Coit DG, Colevas AD, Lacouture ME. Eruptive katoacanthomas associated with pembrolizumab therapy. *DERM*. 2017; 153(7):694-697. doi: 10.1001/jamadermatol.2017.0989.
7. Tidwell WJ, Malone J, Callen JP. Eruptive keratoacanthomas associated with leflunomide Letters. *DERM*. 2016; 152(1):105-106. doi: 10.1001/jamadermatol.2015.2506.
8. Kwiek B, Schwartz RA. Keratoacanthoma: An update and review. *J Amer Acad Dermatol*. 2016; 74(6):1220-1233.
9. Nofal A, Assaf M, Nofal E, Alradi M. Generalized eruptive keratoacanthoma: proposed diagnostic criteria and therapeutic evaluation. *J Eur Acad Dermatol Venereol*. 2014;28(4):397-404. doi: 10.1111/jdv.12226.
10. Grine RC, Hendrix JD, Greer KE. Generalized eruptive keratoacanthoma of Grzybowski: Response to cyclophosphamide. *J Am Acad Dermatol*. 1997; 36(5):786-787. doi: https://doi.org/10.1016/S0190-9622(97)80349-0.
11. Pan A, Reingold RE, et. al. Dermatological adverse events in prostate cancer patients treated with the androgen receptor inhibitor apalutamide. *J Urology*. 2022; 207(5): 1010-1019. doi:10.1097/JU.0000000000002425.
12. Sagawa N, Watanabe, Y, Mizuno, Y, Takahashi S, and Watanabe T. A case of toxic epidermal necrolysis associated with apalutamide administration. *J Cut Immuno Allergy*. 2020; 3(6): 134-135. doi:10.1002/cia2.12138.