DOI: http://dx.doi.org/10.3315/jdcr.2016.1226

Journal of Dermatological Case Reports

Enzalutamide induced acute generalized exanthematous pustulosis

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Keywords:

acute generalized exanthematous pustulosis, drug eruption, enzalutamide, pustular skin eruption, Xtandi®

Abstract

Introduction: *Enzalutamide* (Xtandi®) is a new potent inhibitor of the signaling pathway for the androgen receptor with a half-life of 5.8 days. It has been on the market for the treatment of metastatic castration-resistant prostate cancer since November 2013.

Objective: We report the first case of acute generalized exanthematous pustulosis (AGEP) induced by *enzalutamide*.

Observation: A 62-year-old male patient with no significant medical history, was diagnosed in April 2014 with metastatic prostatic adenocarcinoma. In April 2015 the patient received a second line oral therapy with *enzalutamide*, 160 mg/day, coupled with a subcutaneous implant of 10.8 mg of goserelin, an agonist analog of natural luteinising hormone releasing hormone (LH-RH). Ten days after starting *enzalutamide* treatment and four days after introduction of first goserelin subcutaneous implant, the patient experienced an acute skin reaction. It is about of the plaques covered with widespread millimetric non-follicular pustules. Complete resolution of skin lesions occurred within four weeks. According to the AGEP validation score of the European Study of Severe Cutaneous Adverse Reactions, the total score in the current case was 7, interpreted as probable AGEP. According to criteria that assess adverse drug reactions, it was concluded that *enzalutamide* was responsible for this case of AGEP (suggestive imputation).

Conclusions: Dermatologist can be confronted with adverse skin drug reactions attributable to new therapeutic molecules. The slow resolution of symptoms seems be due to the long half-life of *enzalutamide*. (*J Dermatol Case Rep*. 2016; 10(2): 35-38)

Introduction

Drug-induced acute generalized exanthematous pustulosis (AGEP) is a rare and severe drug eruption, most commonly triggered by antibiotics.[1] *Enzalutamide* (Xtandi®) is a new potent inhibitor of the signaling pathway for the androgen receptor. It has been on the market since November 2013. It is indicated for the treatment of metastatic castration-resistant prostate cancer when treatments with androgen suppression and first-line chemotherapy have failed. The most frequently reported adverse events are asthenia, headache, and hypertension. Adverse events affecting the skin include flushing, skin dryness, and itching.[2,3]

We report the first case of AGEP induced by *enzalutamide*.

Case report

A 62-year-old male patient with no significant medical history, was diagnosed in April 2014 with metastatic prostatic adenocarcinoma. First-line treatment was androgen suppression with *degarelix acetate* and *bicalutamide* plus

chemotherapy (*docetaxel*). In April 2015 the patient received a second line oral therapy with *enzalutamide*, 160 mg/day, coupled with a subcutaneous implant of 10.8 mg of *goserelin*, an agonist analog of natural luteinising hormone releasing hormone (LH-RH). The patient was also given *prednisolone* 40 mg daily for 3 months.

Ten days after starting *enzalutamide* treatment and four days after introduction of first *goserelin* subcutaneous implant, the patient experienced an acute skin reaction. There were large areas of edematous and erythematous plaques (Fig. 1) located on his back, chest, and upper extremities. The plaques were covered with widespread millimetric non-follicular pustules prominent on intertriginous areas, such as the axilla, groin, and trunk. The eruption evolved within four days to diffuse desquamation on the back and arms (Fig. 2) with slightly painful multiple erythematous targetoid papular lesions on his inferior members. He had no mucosal lesions and no fever.

A blood-cell count indicated moderate inflammatory syndrome with peripheral leukocytosis (12.8 G/L; normal range, 4-10), with neutrophilia (10.2 G/L; normal range, 2-7.5), and serum levels of C-reactive protein were increased to 53 mg/L (normal range, <5). Eosinophil number and kidney function were normal. We also noted cholestasis: gamma-glutamyl-transferase to 154 UI/L, normal range: 0-60; and alkaline phosphatase to 707 UI/L, normal range: 40-129.

A skin biopsy showed spongiform intracorneal and subcorneal pustules, edema of the papillary dermis, and an infiltrate with neutrophils and eosinophils in the upper and middle dermis (Fig. 3). A smear from a pustule was sterile.

Acute generalized exanthematous pustulosis (AGEP) was suspected and *enzalutamide* treatment was stopped.[5] The *goserelin* subcutaneous implant could not be removed due to progressive disintegration over 12 weeks (with stable plasma levels).[4,6] Supportive treatment included oral antihistamine, wet dressings, and topical corticoid (*betamethasone valerate*). *Prednisolone* was continued at the same dosage. During eighteen days, mild flare-ups of the skin lesions were noted (Fig. 4) followed by extensive superficial desquamation. Complete resolution of skin lesions occurred within four weeks.

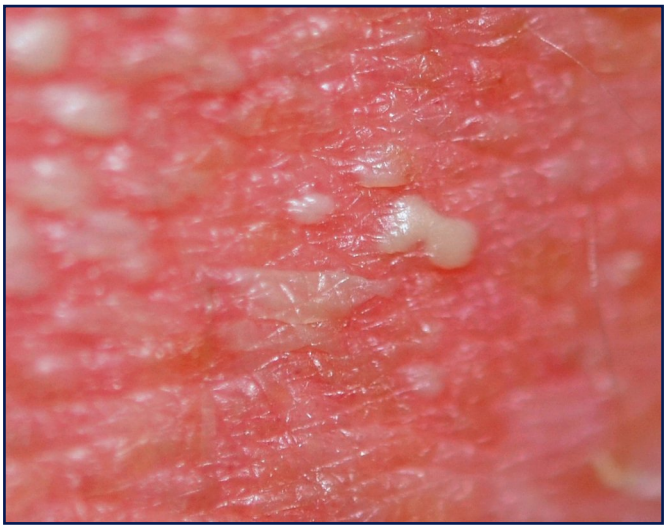

Figure 1
A close-up view showing non-follicular pustules.

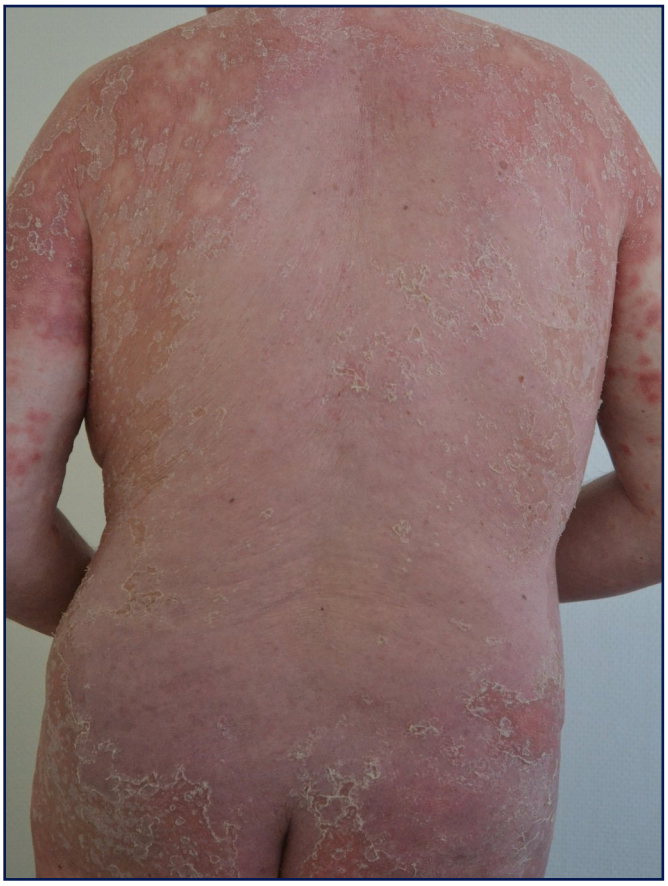

Figure 2
Diffuse erythema and desquamation on the back and arms.

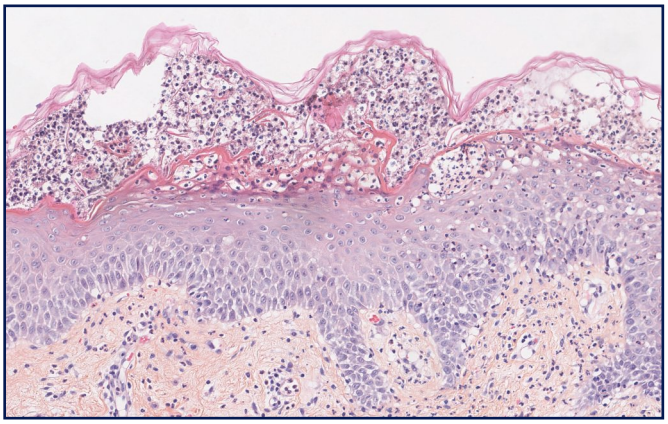

Figure 3
Histological examination (hematoxylin and eosin stain, ×20): intracorneal and subcorneal pustules, spongiosis, and dermal inflammatory infiltrate of neutrophils and eosinophils.

According to the AGEP validation score of the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR),[5] the total score in the current case was 7, interpreted as probable AGEP: pustules, +2; erythema, +2; distribution pattern, +2; post-pustular desquamation , +1; mucosal involvement, 0;

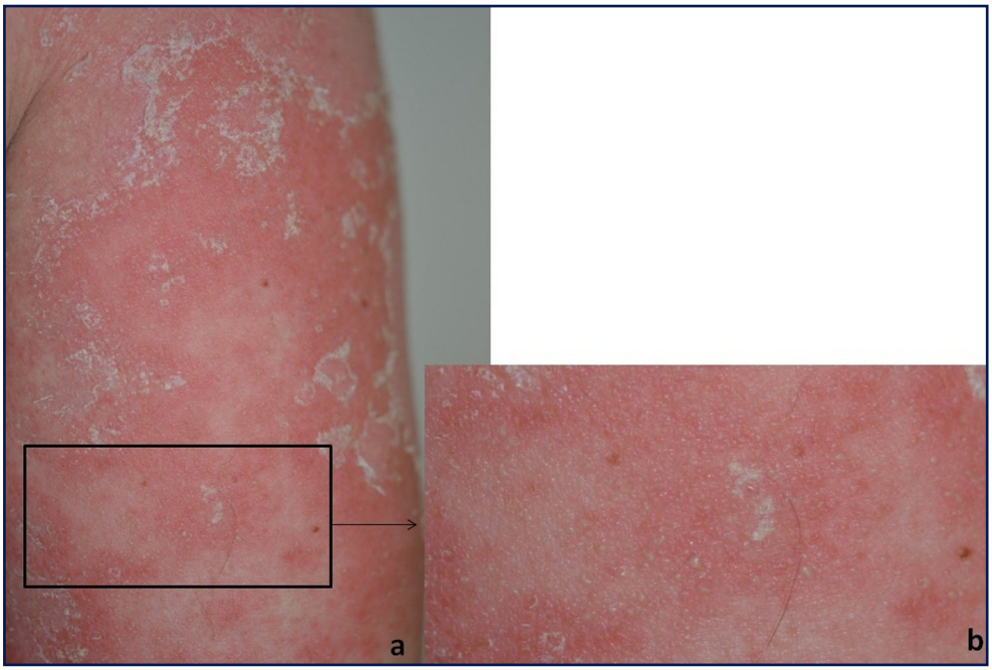

Figure 4
Mild flare-up of skin pustules on the right arm. (a) Diffuse erythema, non-follicular pustules and desquamation; (b) A close-up view showing non-follicular pustules.

acute onset (≤10 days), 0; resolution ≤15 days, -4; fever ≥38°C, 0; blood neutrophil counts above ≥7000/mm^3, +1; histology, +3.

According to criteria to assess adverse drug reactions, *enzalutamide*, rather than *goserelin*, was determined to be responsible for the AGEP.[7]

Discussion

Herein, we present the first case of drug eruption, AGEP, induced by *enzalutamide*. The clinical presentation, biology, histopathologic findings, and time to onset of eruption were consistent with a diagnosis of AGEP caused by *enzalutamide*. This relatively low score for a diagnosis of AGEP (seven) was because of the long period for the eruption to heal (four weeks) and the absence of fever ≥38°C. The eruptions may have taken longer to heal compared to typical cases of AGEP because of the long half-life of *enzalutamide*: i.e., 5.8 days.[8] In fact, the time period of the occurrence of new lesions (eighteen days) corresponds to three half-lives of *enzalutamide*, and the four-week time period needed for complete resolution of eruptions corresponds to five half-lives of *enzalutamide*. According to criteria that assess adverse drug reactions, it was concluded that *enzalutamide* was responsible for this case of AGEP (suggestive imputation).[7]

Subcutaneous implantation of goserelin, because it is surrounded by a biodegradable polymer that provides sustained release of the active principle over a period of 3 months with stable plasma levels,[6] was determined to not be the causative agent for AGEP. In fact, resolution of the eruptions occurred despite the persistence of *goserelin* subcutaneously for 7 further weeks: thus, allowing us to reject its involvement (inconsistent imputation).[7]

The absence of fever ≥38°C and the relatively moderate inflammatory syndrome may be explained by the concomitant administration of 40 mg of *prednisolone* daily.

Conclusion

In everyday practice, dermatologist can be confronted with adverse skin drug reactions attributable to new therapeutic molecules. One particular feature of this case is the slow resolution of symptoms due to the long half-life (5.8 days) of *enzalutamide*.

Acknowledgment

We are indebted to Newmed Publishing Services for English language editing the manuscript.

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