Apalutamide-induced ichthyosiform eruption

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Dear Editor,

Skin eruptions are commonly observed in patients undergoing anticancer therapy, and with the introduction of new drugs in the antitumor treatment landscape evidence regarding their potential cutaneous adverse effects is still building. We herein report the case of an acquired ichthyosiform reaction induced by apalutamide.

A 69-year-old man came to our attention for a one-month-history of a pruritic, scaly, thickened rash involving trunk, limbs and scalp. His medical history revealed a metastatic castration-sensitive prostate cancer (Gleason score of 5+4=9), with metastasis involving adrenal glands, external iliac lymph nodes and pelvic bones. He also suffered from arterial hypertension and atrial fibrillation, which were treated with irbesartan, amlodipine, and dabigatran.

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Key words: apalutamide; drug-induced; acquired ichthyosis; skin reaction; prostate cancer.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Consent for publication: the patient gave his consent for the publication of this case report and any accompanying images.

Received: 18 April 2023.
Accepted: 26 April 2023.

Dermatology Reports 2024; 16:9734
doi:10.4081/dr.2023.9734

The patient had started treatment with gonadotrophin-releasing hormone antagonist degarelix, with subsequent introduction of androgen receptor selective inhibitor apalutamide (240 mg daily), with good response on primary tumor and metastasis. After about two months from the introduction of apalutamide, the pruritic rash occurred.

Skin examination revealed diffuse, dry, rough skin with prominent, polygonal scaling, with more severe involvement of lower legs, forearms and scalp (Figure 1).

No personal or family history of ichthyosis or atopy was reported. No other drugs were added or introduced except for apalutamide. The Naranjo Adverse Drug Reaction Probability Scale score for apalutamide was 5, while the score for the other medications the patient had taken for years was 0. A diagnosis of apalutamide-induced acquired ichthyosis was then suspected and the patient was prescribed with topical emollients and keratolytics. He had moderate improvement in skin lesions with topical therapy and was able to continue anticancer therapy.

Apalutamide is an oral, non-steroidal, second-generation antiandrogen drug, which binds to the androgen receptor, preventing its translocation to the nucleus and subsequent DNA binding.[1]

In phase III, randomized, placebo-controlled TITAN study, the drug significantly improved the overall survival in patients with metastatic castration-sensitive prostate cancer receiving ongoing androgen deprivation therapy when compared to placebo;[2] moreover, in phase III, randomized, double-blind, placebo-controlled SPARTAN study, the drug significantly increased the overall survival in patients with nonmetastatic castration-resistant prostate cancer receiving ongoing androgen deprivation therapy when compared to placebo.[3]

In both studies, skin rash was more common in the apalutamide group compared to placebo. In particular, cases of maculopapular rash, papular rash, generalized rash, butterfly rash, pustular rash, erythema multiforme, lichenoid drug eruptions, stomatitis, and urticaria have been reported during apalutamide treatment.[2,3] Interestingly, Japanese patients were found to be more prone to develop cutaneous adverse events than the global population, still the reasons for this high incidence are poorly understood. In most cases, the skin rash occurred within four months of apalutamide treatment and was easily managed with topical/systemic corticosteroids or oral antihistamine, with or without dose adjustment.[4]

Furthermore, Miyagawa *et al*. reported the first case of a psoriasiform eruption occurring after apalutamide treatment, highlighting that sex hormone imbalances may be a trigger of psoriasis.[5]

To the best of our knowledge, this is the first report of an acquired ichthyosiform reaction induced by apalutamide. Nonetheless, the casual connection and the underlying pathogenetic mechanisms should be confirmed and strengthened by new case series and studies.

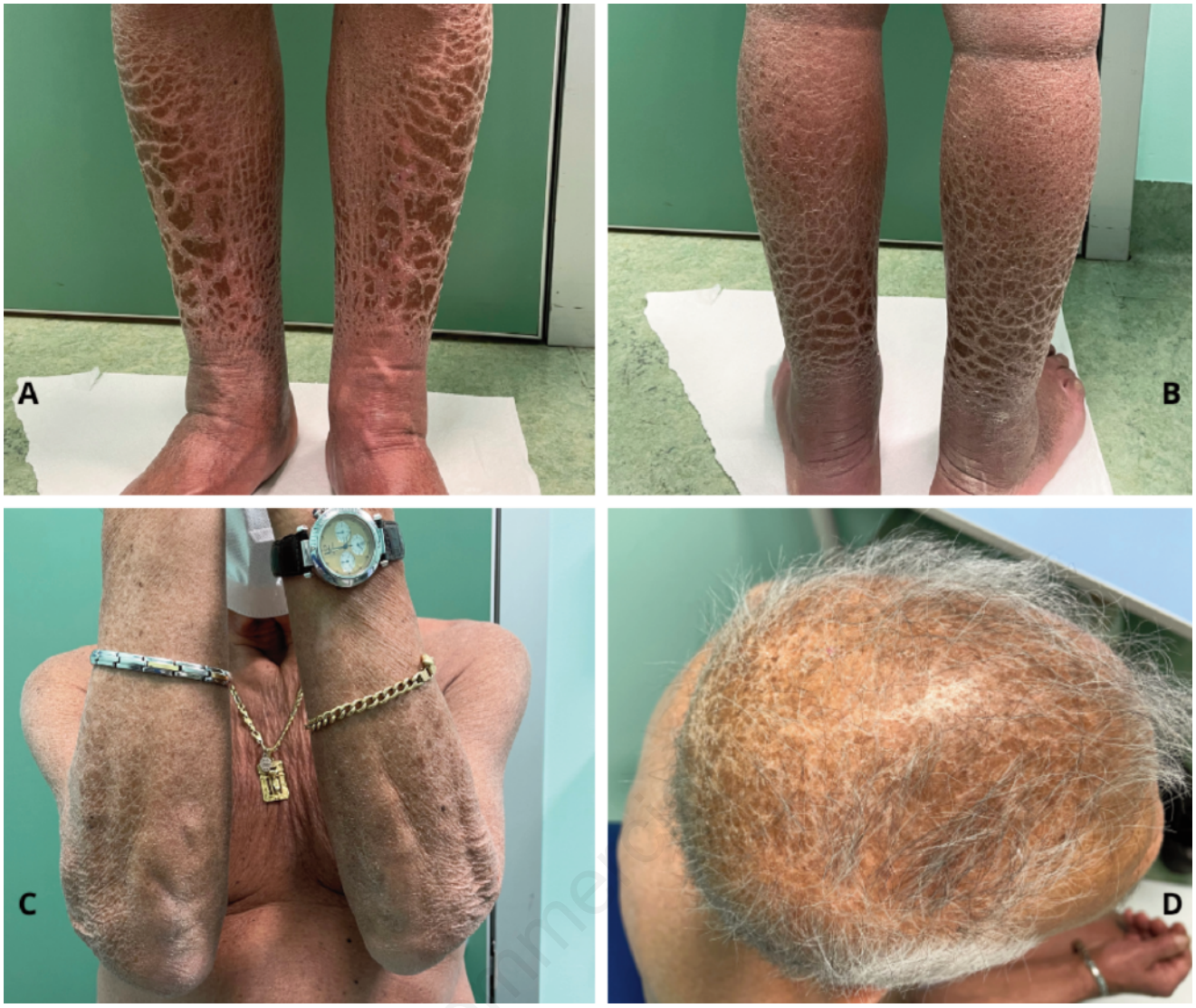

Figure 1. Diffuse, prominent, polygonal scaling is evident on lower legs (**A, B**), forearms (**C**), and scalp (**D**).

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