SHORT COMMUNICATION

Cutaneous Adverse Reactions to Apalutamide: Case Series with Clinical and Pathological Correlations

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Apalutamide is a novel non-steroidal, second-generation, selective competitive inhibitor of the androgen receptor approved for the treatment of non-metastatic castration-resistant and metastatic hormone-sensitive prostate cancer (1). Adverse cutaneous reactions (ACRs) to apalutamide have been described in 23.8–27.1% of patients in clinical trials, with 5.2–6.3% grade-3 ACR according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) (1–4). However, the precise clinical presentation, the histopathological correlation, and the underlying mechanism of ACRS to apalutamide are poorly understood.

Here, we aimed to describe the clinicopathological features of ACRS to apalutamide in a case series of 9 patients.

MATERIALS AND METHODS (see Appendix S1)

RESULTS

The study was conducted according to guidelines from the local institutional Review Board and the Declaration of Helsinki.

Of 121 PCP treated with apalutamide in our institution, 24 patients (19.8%) presented an ACR to the treatment. Due to the extension and/or clinical impact (non-tolerable grade 2 or superior), 11n patients were referred to the dermatology department. Median age of presentation was 77.7 years (range, 65–90). One patient had a personal history of mild psoriasis, without flares since youth. The median latency of onset was 112.9 days (range, 43–223 days). The clinicopathological features are summarized in Table SI.

All presented a maculopapular rash (Grade 2–3) involving a range of 20–90% of total body surface area; none presented mucosal lesions. Four patients had an eczematous rash, 3 a lichenoid aspect (**Fig. 1**B) and 2 were non-specific. One patient with an exfoliative erythroderma required admission, monitoring, and systemic steroids, with complete recovery (Fig. 1C). Patients reported moderate to severe pruritus but did not present any other systemic symptom (pain, fever, hypotension).

Cutaneous biopsy was obtained from 8 patients. Two patients had a lichenoid interface dermatitis (**Fig. 2**A–B), one of which was accompanied by abundant eosinophils. Four patients had a spongiotic dermatitis and 2 patients had a mixed spongiotic and lichenoid dermatitis (Fig. 2C–D).

A blood sample was obtained from 6 patients: 4 patients exhibited eosinophilia (700–2,000x10^9 eosinophils/L). In the characterization of the ACRs, *in vitro* lymphocyte proliferation test (LPT) to apalutamide was positive in 3 patients (3/9). Apalutamide patch tests readings at day 2 and day 4 were negative in the 7 patients tested.

All patients received topical corticosteroids and oral antihistamines, with 6 requiring oral corticosteroids. The ACR led to the discontinuation of treatment in 6 patients. In 3 patients in whom apalutamide was reintroduced, no subsequent ACR appeared. All patients had a complete resolution. Despite this, 2 patients had a post-inflammatory hyperpigmentation and 1 patient marked xerosis.

DISCUSSION

ACR to apalutamide are common, although the pathogenesis remains elusive. This study provides significant novel data regarding the clinicopathological presentation and potential delayed hypersensitivity as the underlying mechanism.

The incidence of ACR in our cohort was 19.8%, similar to SPARTAN and TITAN clinical trials (1, 3, 4), as well as grade-3 ACR incidence (5%). In previous studies, low bodyweight has been associated as a predictive factor with the incidence of ACR (5), without other significant clinical factors for the incidence, worsening, and recur-

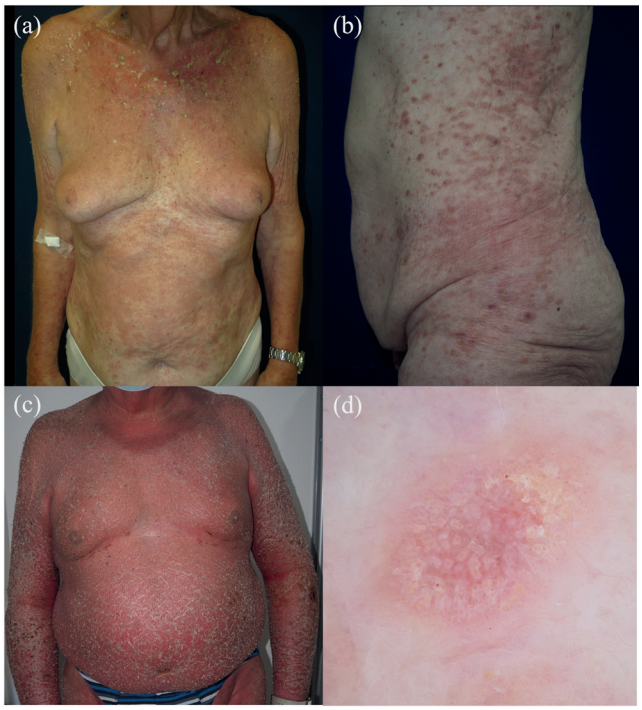

Fig. 1. Clinical spectrum of cutaneous adverse reactions to apalutamide treatment in prostate cancer patients. (A) Maculopapular confluent exanthema, with crusting and marked erythema in the neckline. (B) Maculopapular non-confluent lichenoid-like exanthema, affecting predominantly the lateral regions of the trunk. (C) Exfoliative erythroderma with marked desquamation. On dermoscopy (D), a white pseudo-reticular structure, corresponding to Wickham-like striae, with dotted vessels could be observed.

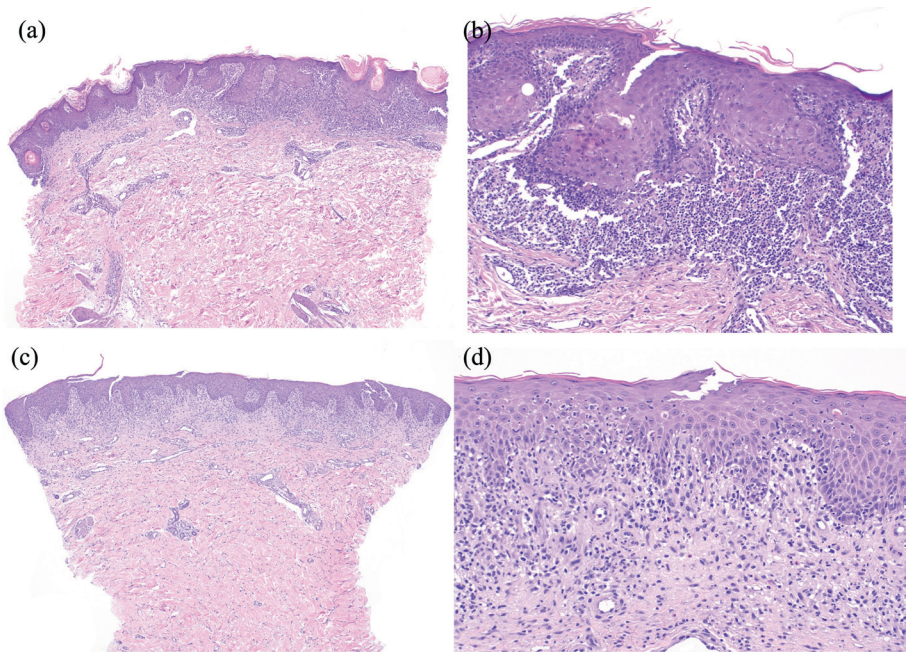

Fig. 2. Histological spectrum of cutaneous adverse reactions to apalutamide treatment in prostate cancer patients. (A, B) Lichenoid interface dermatitis with a dense dermal-band infiltrate with colloid bodies and without eosinophils. (C, D) Subacute spongiotic dermatitis with marked spongiosis with lymphocytic exocytosis. In the papillary dermis, a mixed infiltrate composed of lymphocytes, neutrophils, and eosinophils could be observed.

rence of ACR (2, 3, 6). Median latency of onset in our study was longer than in previous studies (112.9 vs 80–82 days) (2, 3). Katsuta et al. (7) described in a recent review of the literature that no SCARS to apalutamide appeared ≥8 weeks. Despite that, in this study, 1 patient had an exfoliative erythroderma 108 days after apalutamide initiation.

ACRs in apalutamide clinical trials were predominantly reported as nonspecific dermatological presentation, such as "rash", "urticaria", or "blisters" (2). In our study, the patients presented either a violaceous lichenoid exanthema or an acute eczematous dermatitis. The kind of dermatitis, along with the extension, led to different dermatological management. One patient presented a more severe exfoliative erythroderma (DRESS Regiscar=2, possible). In the literature, isolated case reports of DRESS (8, 9), toxic epidermal necrolysis (TEN) (10), and acute generalized exanthematous pustulosis (AGEP) (11) have been described.

Histologically, spongiotic, lichenoid, or mixed histological patterns were observed, which shows its diversity. Except for 1 patient, eosinophils were abundant in most skin biopsies, which supports a sort of hypersensitivity mechanism as pathogenesis. Histological descriptions of this ACR in the literature are scarce, except for reports of SCARS, with 2 previous report of 2 patients presenting a spongiotic dermatitis (12) and 1 reporting an ACR with lichenoid features (13).

Mechanism of apalutamide ACR is not well defined. Previous studies have postulated that these reactions may be dose-dependent (14) and that dose reduction could potentially lead to clinical improvement. In fact, apalutamide plasma concentration had been found to be numerically higher in patients with an ACR, but this did not reach statistical significance (2). This would explain why low bodyweight is a risk factor for ACR development. We could demonstrate that, at least in part, some cases could be explained by development of delayed hypersensitivity to apalutamide. However, the reason why most cases do not present positive LPT, and none of them positive patch testing, remains elusive. The metabolism of apalutamide results in the formation of different metabolites. N-desmethyl apalutamide (M3) is the major one, which contributes to one-third of the clinical activity of apalutamide. The role of these metabolites in the development of a drug reaction is unknown and could be the reason for the negativity in patch testing. Overall, non-standardization of LPT and no use of controls for patch testing, as well as metabolism transformation of apalutamide, may limit the use of LPT and patch testing to prove a delayed immune response to apalutamide.

As the frequency of ACR is much higher with apalutamide than with any other antiandrogens, some authors have postulated it is related to a structure-specific non-related to the mechanism of action. In fact, despite enzalutamide and apalutamide sharing up to 70% of chemical structure, as opposed to flutamide and bicalutamide, the prevalence of ACR to enzalutamide is much lower (2.4%) (15). Ji et al. (16) proved in animals models that the 2-cyanopyridine moiety in apalutamide, not present in enzalutamide, may react with cysteine in proteins forming haptens and triggering a T-cell mediated immune response. These findings would support a delayed-onset hypersensitivity reaction as the main mechanism of action, along with the clinical presentation (delayed onset, responsiveness to corticosteroids, and recurrence after drug exposure) (16). In our study, LPT was positive in only 3 out of 9 patients. Interestingly, a previous study showed that LTT was positive in 4 out of 4 severe cases (3 TEN, 1 AGEP) and only positive in 2 of 7 (28.6%) in milder cases (7). Therefore, the mechanism of ACR to apalutamide might be multifactorial and not

only explained by a delayed hypersensitivity reaction, especially in milder cases.

In this study, all patients had *ad integrum* evolution without significant sequelae. Despite this, ACR led to the complete discontinuation of treatment in 5 out of 9 patients. In apalutamide clinical trials, treatment discontinuation due to cutaneous toxicity was present in 8.5–9.9% of patients (1, 4). Such differences might be explained by the fact that most grade 1–2 ACR resolved with topical therapy and were managed by the urology department without dose interruption or reduction, and that the patients in this series were highly selected due to the severity of the clinical presentation. In fact, in our whole cohort, no other patient discontinued apalutamide due to skin toxicity, having an overall prevalence of treatment discontinuation due to ACR of 4.1%. Dose reduction was a frequent therapeutic option in other studies (11.5–19.7% [1, 4]), although we used it in only 2 patients, and has been proved to be an effective preventive measure, especially in small body sizes, allowing lower rates of overall ACR and grade-3 ACR, without impacting on overall survival of PCP (17, 18). PCP response to apalutamide can be monitored through clinical exploration, PSA levels, and imaging studies, while apalutamide therapeutic drug monitoring is not used in clinical practice.

Of the 3 patients in whom apalutamide was not discontinued, none presented further ACR. In previous studies, recurrence of apalutamide ACR has been described in up to 45.2% of patients who resumed apalutamide (6) with a potential worsening in posterior flares (3).

In conlcusion, apalutamide is associated with a variable spectrum of severity and type of ACRs, mainly spongiotic and/or lichenoid dermatosis, that can appear after months of treatment. In our experience, grade-3 ACR frequently implied treatment discontinuation. Despite supporting evidence in the literature of a structural-specific induced hypersensitivity response in animal models, in our series LPT suggested this mechanism in one-third of patients. The risk of maintaining the treatment and the available therapeutic oncological alternatives must be agreed on an individual basis to avoid a detrimental oncological impact on survival. Dose reduction or titration might be a good preventive or therapeutic alternative in mild cases (grade 1–2 ACR) without impacting the oncological control, but the risk–benefit ratio should be considered in severe cases as SCAR cannot be ruled out.

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The study has been approved by the institutional review board guided by the STROBE checklist.

The patients have given written consent for publication and use of clinical photographs and medical information.

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