

LETTER TO THE EDITOR

Cutaneous adverse reactions associated to apalutamide: two case reports of DRESS syndrome and maculopapular exanthema

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Apalutamide, an oral androgen receptor signaling inhibitor approved for the treatment of prostate cancer, has been associated with frequent occurrence of cutaneous adverse events (CAE) during pivotal SPARTAN and TITAN studies, in 24% and 27% of the patients, respectively [1, 2]. However, side effects are gathered under the umbrella term ‘rash’, which can encompass a wide number of dermatoses with various prognosis. Post-marketing follow-up usually allows a better classification of those CAE. Apalutamide is mainly responsible for benign maculopapular exanthema (MPE), xerosis, lichenoid reactions [3–5]. But potentially life threatening condition such as acute generalized exanthematous pustulosis [6], DRESS [7, 8] or toxic epidermal necrolysis [3] have been described in the literature. We report two cases from our clinic illustrating the clinical spectrum of the CAE.

Case 1. A 70-year-old man with numerous comorbidities including hypertension, hypercholesterolemia, DM2 and diabetic nephropathy, chronic obstructive pulmonary disease, sleep apnea, and lower limb arteriopathy had been diagnosed with Stage IV B prostate adenocarcinoma, lymph nodes and bone metastases in early 2023. Castration-treatment with GnRh-blocker (Degarelix) had been initiated in February 2023 followed with GnRH-agonist (Leuprolin) in March 2023 in association with apalutamide (240 mg once daily). Other medical treatments had been ongoing and unmodified except for GLP-1 agonist dulaglutide, which was also started in the end of March 2023 a couple of weeks after apalutamide.

In the beginning of July, he developed an itchy and scaly rash of the face, upper limbs and trunk associated with edema of the face and hands. At the time, dulaglutide was suspected of being the culprit and was discontinued. His general condition worsened rapidly, and he was hospitalized because of acute kidney failure, hypotension and oliguria. Upon presentation, he had fever (38 °C) and displayed scaly erythroderma (erythema over 80% of the body surface). He had enlarged peripheral lymph nodes in the axillary folds and groins, but no hepatosplenomegaly. Laboratory findings include elevated eosinophilia (6,770/mm³), monocytosis (1,113/mm³) kidney failure (creatininemia 335 micromol/mL, glomerular filtration

rate 15 mL/min/m²) and marked inflammation with elevated CRP 103 mg/L and thrombocytosis (572,000/mm³). Liver enzymes were within normal ranges. HHV6 viremia was not analyzed. EBV and CMV reactivation was ruled out. Histological examination of a skin biopsy showed a spongiotic epidermis and an inflammatory infiltration of the dermis by lymphocytes and numerous eosinophils. Diagnosis of DRESS reaction to apalutamide was made, in the lack of reported case of DRESS with dulaglutide. Systemic corticosteroid was initiated. The patient remained hospitalized for over a month.

Case 2. A 72-year-old man with prostate cancer was referred in February 2022 in emergency for an acute exanthema that started 1 week before presentation. His medical history was only notable for prostate adenocarcinoma (pT2 Gleason 3 + 4 = 7). Robot assisted laparoscopic prostatectomy had been performed 10 months ago. Increase in PSA values during 2023 and detection of bone metastases prompted to initiate hormonal therapy. Degarelix (1 month depot) was started 1 month and apalutamide 1 week before rash onset. Upon presentation, the patient had a maculopapular exanthema that affected over 80% of the body surface. There were no target-like lesions, no blisters, no pustules. Nikolsky sign was negative and mucosae were spared. He presented transient fever and small peripheral lymph nodes were palpated in the axillae. Punch skin biopsy analysis showed an interface dermatitis associated with eosinophils confirming a drug-induced rash. Laboratory findings included a transient increase of eosinophils 780/mm³ and transient elevation of liver enzymes (ALAT 146, 3 × N, N < 50 U/L). He was diagnosed with a grade 3/NCI-CTCAE 3 maculopapular exanthema due to

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apalutamide and discharged home under oral corticosteroid (prednisolone 0.5 mg/kg daily, 40 mg) that was quickly tapered over the month.

We report two cases of CAE with apalutamide. In the first case, the patient developed DRESS syndrome. DRESS is a rare but potentially life-threatening CAE characterized by a long-time interval from first drug exposure to symptom onset (2 weeks to months from drug initiation), a prolonged course, often with flares, even after discontinuation of the causal drug. The pathophysiology of DRESS syndrome remains incompletely understood but involves reactivation of herpes viruses (HHV-6, HHV-7, EBV, and CMV), a strong antiviral immune response and specific HLA groups [9]. Diagnostic criteria for DRESS syndrome have been defined including clinical symptoms such as high fever, enlarged peripheral lymph nodes, skin involvement, facial edema, other organ involvement and eosinophilia. Usual drugs responsible for DRESS include allopurinol, anticonvulsants, and antibiotics. Apalutamide has been reported in two previous DRESS cases. DRESS developed 39 days [7] and 30 to 45 days after initiation [8]. In our case, the rash developed 3 months after drug initiation. CAE during apalutamide display rather long delay [3, 5, 10]. Katsuta found that patients with severe CAE had a shorter mean onset time than patients with moderate CAE, 5.2 weeks and 9.6 weeks, respectively [10]. However, it is noteworthy that some cases of CAE have been diagnosed as MPE, despite high eosinophilia and late onset of symptoms, both suggesting the possibility of DRESS [3, 4]. Not all cases with eosinophilia fall in the DRESS diagnostic. According to Pan et al., 6% of the patients with CAE had eosinophilia within 2 weeks of CAE incidence. In case 2, the patient presented with a typical EMP of rapid onset after initiation of the drug and transient eosinophilia that resolved rapidly with oral corticosteroids. Local recommendations for the management of apalutamiderelated CAE have been published [5]. In case of MPE, according to CTCAE grading, apalutamide can be maintained or halted and active treatment include high potency topical corticosteroid and oral antihistamine, or oral corticosteroids. Rechallenge at decreased dose can be attempted in some situation or the urologist can ask for dermatologic advice. In the case of DRESS, apalutamide should be definitively withdrawn.

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