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Case Report

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Severe Toxicodermia due to Apalutamide: A Case Report of DRESS in an Elderly Adult

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ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe toxicoderma characterized by a hypersensitivity reaction to medications, accompanied by eosinophilia and systemic manifestations. Apalutamide, a selective androgen receptor inhibitor approved for the treatment of prostate cancer, has been associated with various dermatological complications. This study documents the clinical case of an 81-year-old geriatric patient with stage IV acinar adenocarcinoma of the prostate who developed toxicoderma four weeks after initiating apalutamide.

The patient presented with a 15-day history of generalized papular lesions and malaise that did not improve with oral antihistamines. Physical examination revealed facial edema and erythema, along with desquamative erythematous-edematous plaques covering more than 50% of the body surface area. Laboratory findings showed eosinophilia (3040 cells/µL) and a rise in baseline creatinine from 1.76 mg/dL to 2.4 mg/dL. The RegiSCAR score was 3 points, classifying this as a possible case of DRESS. A skin biopsy demonstrated a dermoepidermal hypersensitivity reaction with eosinophilic infiltration.

The patient improved with oral and topical corticosteroids and discontinuation of apalutamide, confirming the diagnosis of DRESS. He remains under follow-up by the Oncology service.

Given that numerous medications have been implicated in DRESS syndrome, early recognition is critical. Prompt identification allows for the suspension of the causative agent, reducing morbidity and mortality. Furthermore, it facilitates timely modification of oncological therapy in advanced-stage patients, ensuring that cancer management is not compromised.

Keywords: Apalutimide; Chemotherapy; DRESS; Drug reaction; Toxicodermia

INTRODUCTION

With the increasing use of novel chemotherapeutic agents, severe cutaneous adverse reactions are being reported more frequently[1]. DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) commonly presents as a morbilliform rash accompanied by fever and lymphadenopathy, typically appearing 2 to 8 weeks after drug initiation. Early recognition and intensive treatment are essential given the associated high mortality[2].

Apalutamide, an androgen receptor inhibitor used in prostate cancer hormone therapy, is frequently associated with the development of a skin rash shortly after treatment initiation[3]. However, severe toxicodermias such as DRESS syndrome remain rare, with most reported cases occurring in Asian patients[4]. Herein, we present the clinical profile of an elderly Colombian patient diagnosed with stage IVa acinar prostatic adenocarcinoma who developed DRESS syndrome following apalutamide therapy.

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Case presentation

An 81-year-old African American man was diagnosed with metastatic prostate cancer involving the bone and lymph nodes, with a PSA level of 100 µg/L. Given his limited healthcare access, the oncology team added apalutamide 240 mg daily to his existing regimen, which included goserelin. His medical history was notable for arterial hypertension, managed with losartan 100 mg daily and nifedipine 60 mg daily. He had no known drug allergies.

Four weeks after starting apalutamide, the patient developed an erythematous maculopapular rash that began on his legs and spread to his back, abdomen, and upper extremities. Associated facial edema and fever prompted an emergency department visit. On physical examination, the rash involved approximately 60% of his body surface area (BSA), with no skin detachment. Facial edema was evident, but the oral mucosa was spared (Figure 1).

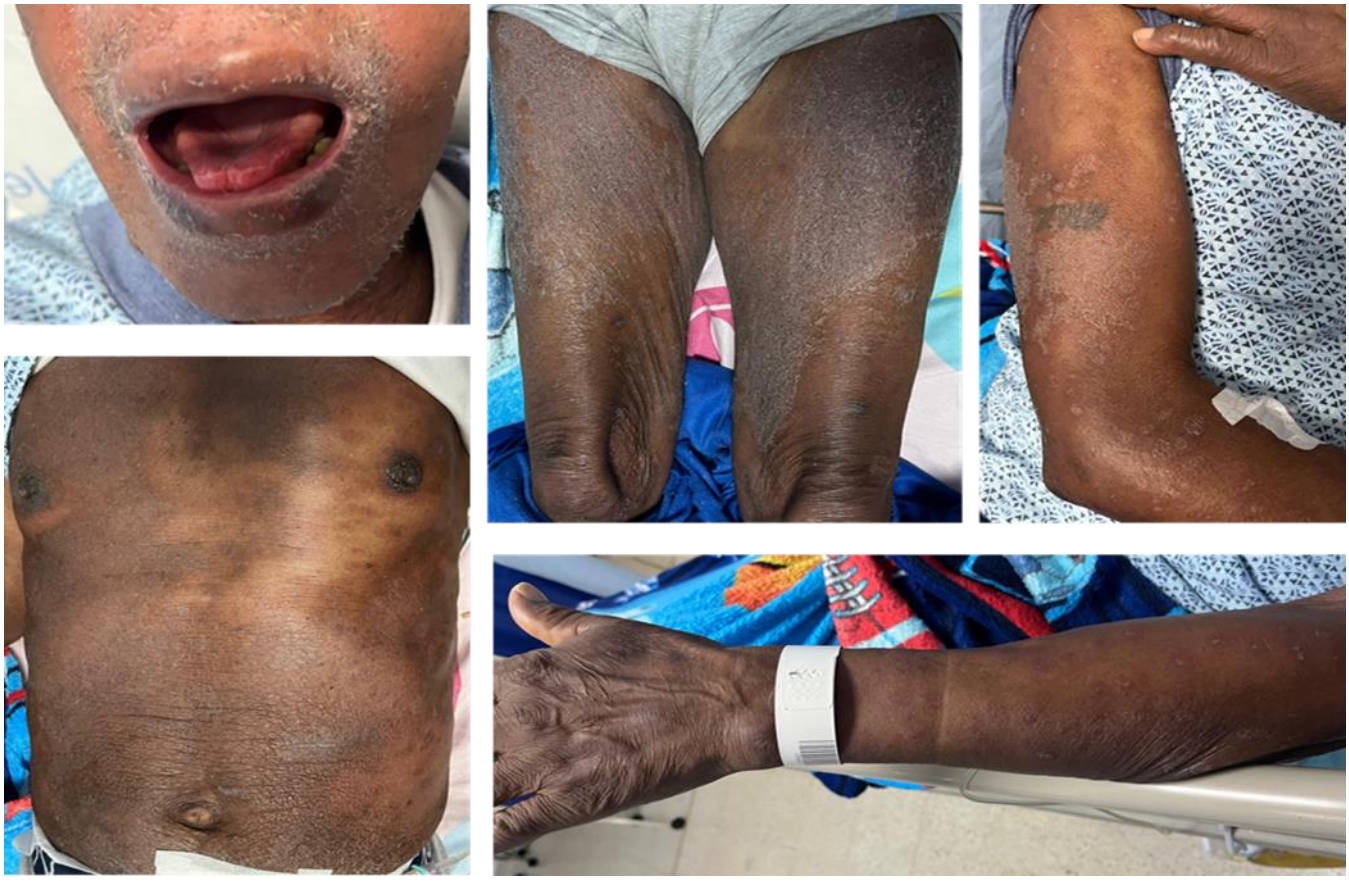


Figure 1. Shows lip edema without involvement of the oral cavity, along with an erythematous maculopapular rash on the trunk, legs, arms, and forearms

Initial laboratory findings revealed an eosinophil count of 1.3 × 10^9/L and a rise in serum creatinine from 1.76 mg/dL to 2.4 mg/dL, with no elevation in transaminases or other laboratory abnormalities. The RegiSCAR score was 3 points, classifying the case as possible DRESS (Table 1). The dermatology team initially assessed the condition as a severe cutaneous drug eruption, likely attributable to apalutamide. Following deworming with ivermectin to rule out strongyloidiasis, the patient was started on prednisone at 1 mg/kg, and apalutamide was discontinued.

Table 1: RegiSCAR scoring items applied to the present case

RegiSCAR item	Patient finding	Score
Fever ≥38.5°C	39°C at presentation	0
Enlarged lymph nodes (≥2 sites)	Absent	0
Eosinophilia	1.3 × 10⁹/L (700–1499/μL)	+1
Atypical lymphocytes	Not reported	0
Rash extent >50% TBSA	≈60% TBSA	+1
Rash typical of DRESS	Facial edema and infiltrated erythema	+1
Skin biopsy compatible with DRESS	Compatible histology reported	0
Internal-organ involvement	Renal impairment (creatinine rise)	+1
Prolonged course ≥15 days	Not documented	−1
Alternative causes excluded	Not fully documented	0
Total	Possible DRESS	3

A skin biopsy of the right forearm was performed the following day. Histopathological examination revealed small foci of spongiosis and vacuolization at the dermoepidermal junction, scattered apoptotic cells, and a mild perivascular inflammatory infiltrate (Figure 2). These findings were consistent with a dermoepidermal hypersensitivity reaction with eosinophilia, further supporting the diagnosis of DRESS.

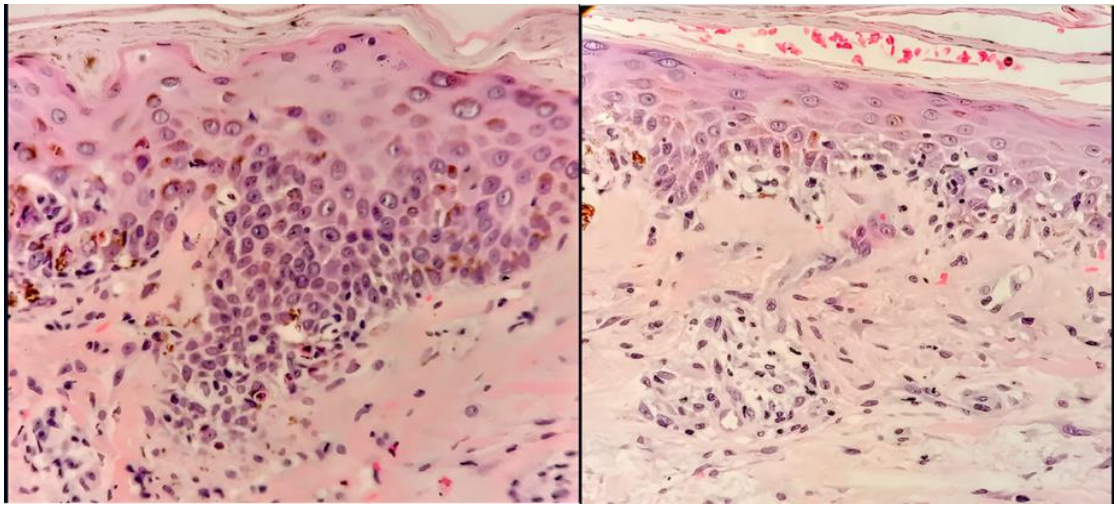


Figure 2. Skin biopsy reveals small foci of spongiosis with vacuolization at the dermoepidermal junction and scattered apoptotic cells, along with a sparse perivascular inflammatory infiltrate

In this case, the reaction was considered moderate in severity due to renal involvement in the absence of multi-organ failure, significant transaminase elevation, or respiratory or cardiac compromise.

During the next five days of hospitalization, the rash began to subside, and corticosteroids were tapered to prednisolone 5 mg daily. The patient was discharged for outpatient follow-up, during which his skin gradually stabilized. Apalutamide was permanently discontinued. He is currently receiving leuprolide acetate every six months, with no new episodes of rash or other dermatologic complications.

DISCUSSION

DRESS syndrome is an idiosyncratic, potentially life-threatening drug reaction[2,5]. It was first described in association with antiseizure medications such as lamotrigine, phenytoin, and carbamazepine, but has since been linked to numerous other drugs, including antibiotics, antivirals, and gout medications[5]. Diagnosing DRESS can be challenging, and many cases may go unrecognized and untreated[2]. In the present case, DRESS was associated with the recent initiation of apalutamide for prostate cancer; early suspicion enabled prompt treatment and rapid withdrawal of the offending agent.

DRESS presents with a highly variable clinical picture, reflecting a wide spectrum of cutaneous eruptions and organ involvement [5,6]. Classic features include a severe skin eruption, fever, eosinophilia, lymphadenopathy, internal organ involvement, and hematological abnormalities such as atypical lymphocytes 6. Symptom onset typically occurs 2 to 8 weeks after drug exposure, and the condition may progress even after the offending agent is withdrawn[5]. In our patient, characteristic erythematous lesions and fever were present, though lymphadenopathy was absent. Consistent with the typical 2- to 8-week window, eosinophilia and renal involvement appeared four weeks after apalutamide initiation, which prompted immediate consideration of DRESS.

When DRESS is suspected—even with incomplete clinical manifestations—patients can be classified using the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system into categories ranging from "no DRESS" to "definite DRESS"[7]. The Japanese consensus group criteria, which include Human Herpesvirus 6 reactivation, have also been described; however, comparative analyses have shown that the Japanese criteria have lower sensitivity for diagnosing definite or probable DRESS than the RegiSCAR criteria[8]. Applying the RegiSCAR system to our patient, who scored 3 points and was classified as having possible DRESS, corticosteroids were initiated immediately upon emergency department admission.

Although DRESS is considered an idiosyncratic reaction, HHV-6 reactivation is detectable in up to 63% of cases and should be investigated[9]. It is also essential to rule out other conditions with overlapping presentations, such as autoimmune disease, infection, or viral hepatitis. Accordingly, patients with suspected DRESS should have negative antinuclear antibodies, negative blood cultures, and negative serologies for hepatitis A, B, and C[6].

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In the SPARTAN and TITAN trials, which evaluated apalutamide for prostate cancer, rash and xerosis were common but rarely led to dose reduction or discontinuation[11,12]. No cases of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) were reported in these studies[11]. However, we identified two additional cases of DRESS associated with apalutamide[13,14].

Pharmacokinetic studies have shown that apalutamide has a long half-life, ranging from 110 to 231 hours[15]. Given this, prompt discontinuation should be considered when a drug reaction is suspected, noting that symptoms may progress despite drug withdrawal[5]. In our patient, pulse corticosteroid therapy was administered for three days, followed by a gradual oral taper, and apalutamide was discontinued.

In our review of apalutamide-associated severe cutaneous adverse reactions, we identified three published DRESS cases, with a typical latency of 4–5.5 weeks after drug initiation—similar to our case. The patients were also older men (77–85 years). These cases resolved after immediate drug withdrawal and showed marked clinical improvement following corticosteroid therapy 16–18. A structured comparison with previously reported cases is provided in Table 2.

Table 2: Comparison of published apalutamide-associated DRESS cases and the present case

Source	Patient demographics	Underlying disease / comorbidities	Latency (weeks)	Clinical/lab features	Treatment	Outcome
Present case	81M, African descent	Metastatic prostate cancer; HTN	4	Maculopapular rash ≈60% TBSA, facial edema, fever; eosinophils 1.3×10^9/L; renal impairment	Apalutamide stopped; systemic corticosteroids; topical therapy	Improved; discharged after 5 days; steroid taper
Ducharme et al. (Contact Dermatitis 2022)[16]	85M, Caucasian	Castration-resistant prostate cancer; hypertension	5.5	DRESS; biopsy: apoptotic keratinocytes, dermal eosinophils	Systemic steroids 0.5 mg/kg/day	Recovered
Hsu et al. (JEADV) – case 1 summarized in Flynn et al.[18]	85M, Taiwanese	NR	4	DRESS with possible SJS overlap; biopsy: severe interface dermatitis/epidermal necrosis	Methylprednisolone	Recovered
Hsu et al. (JEADV) – case 2 summarized in Flynn et al.[18]	77M, Taiwanese	NR	5.5	DRESS with possible SJS overlap; biopsy: severe interface dermatitis/epidermal necrosis	NR	NR
Martin et al. (Cureus 2023)[17]	74M, NR	Prostate cancer; HTN	≈4–6	Rash, fever, facial edema, lymphadenopathy; marked eosinophilia; biopsy compatible	Drug discontinued; systemic corticosteroids; antihistamines	Improved

NR: not reported. Data for Hsu cases are summarized from the literature review in Flynn et al.

CONCLUSION

DRESS syndrome is a rare drug reaction associated with significant mortality. Prompt identification of the causative agent and early initiation of appropriate treatment are essential to reduce long-term morbidity. Since apalutamide is already associated with frequent rashes and other cutaneous reactions, prostate cancer patients receiving this hormonal therapy should be closely monitored for such adverse events.

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