Case Reports in Oncology

Case Rep Oncol 2023;16:646–655
DOI: 10.1159/000532009
Received: May 1, 2023
Accepted: July 5, 2023
Published online: August 16, 2023

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Case Report

Apalutamide-Induced Toxic Epidermal Necrolysis in a Caucasian Patient with Metastatic Castration-Sensitive Prostate Cancer: A Case Report and Review of the Literature

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Keywords
Apalutamide · Case report · Prostate cancer · Drug therapy · Toxicity

Abstract
Apalutamide is a novel nonsteroidal androgen receptor inhibitor that has been shown to improve outcomes for patients with nonmetastatic castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer when combined with androgen deprivation therapy. Apalutamide-induced skin rash occurred commonly in clinical trials, with 23.8–27.1% of patients experiencing a rash of any grade, and 5.2–6.3% experiencing a rash of grade three or higher. There were no cases of severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) reported in clinical trials; however, there are rare cases reported in the literature with the majority occurring in Asian patients. An 83-year-old Caucasian male was commenced on apalutamide, combined with degarelix, for the management of metastatic castration-sensitive prostate cancer. During week five of apalutamide treatment, the patient developed a widespread erythematous maculopapular rash. On presentation, the rash affected 80% of his body surface area (BSA) and a diagnosis of a severe cutaneous drug eruption was made. He was commenced on methylprednisolone (MP) therapy. Despite 5 days of MP, the rash continued to deteriorate involving 95% of his BSA. Nikolsky's sign was positive. A diagnosis of overlap SJS/TEN was made, supported by skin biopsy. His SCORTEN score was three. He was then commenced on intravenous immunoglobulin and transferred to the intensive care unit. Over the coming days, the rash began to stabilise, and his steroid dose was weaned. He was discharged from hospital 38 days after rash onset. We report the first

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suggested case of apalutamide-induced SJS/TEN in a Caucasian patient. We discuss other cases of apalutamide-induced SCARs reported in the literature. Risk factors seem to include low body weight and Japanese race, as well as short time to onset of rash.

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Introduction

Apalutamide is an oral, novel, nonsteroidal competitive inhibitor of the androgen receptor (AR) that works by binding directly to its ligand-binding domain. This prevents translocation of AR from the cytoplasm into the nucleus and inhibits AR-dependent gene transcription [1]. Apalutamide combined with androgen deprivation therapy (ADT) was first shown to be an effective treatment for men with nonmetastatic castration-resistant prostate cancer in the SPARTAN trial, with a significant improvement in metastasis-free survival and time to symptomatic progression with apalutamide versus placebo [2]. Apalutamide was then demonstrated to significantly improve overall survival and radiographic progression-free survival when combined with ADT for men with metastatic castration-sensitive prostate cancer in the TITAN trial [3].

Apalutamide was reasonably well tolerated in both the SPARTAN and TITAN trials. In SPARTAN, the two most common apalutamide-related adverse events were fatigue (30.4% vs. 21.1%) and rash (23.8% vs. 5.5%), with 5.2% in the apalutamide group developing a rash of grade 3 or higher. Nineteen patients (2.4%) discontinued apalutamide, and 22 patients (2.7%) required dose reduction secondary to rash [2]. Similarly, in TITAN, rash of any grade occurred in 27.1% of patients on apalutamide versus 8.5% on ADT alone, with 6.3% developing a rash of grade 3 or higher. Skin rash led to discontinuation of apalutamide in 12 patients (2.3%) and dose reduction in 28 patients (5.3%) [3]. The median time to onset of skin rash was 82 days in SPARTAN and 81 days in TITAN. There were no reported events of drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in either trial.

Rare cases of apalutamide-induced severe cutaneous adverse reactions (SCARs) including DRESS and SJS/TEN have been reported in the literature, with the majority of these occurring in Asian patients. Here, we report a case of apalutamide-induced overlap SJS/TEN in a Caucasian patient receiving apalutamide combined with degarelix for the management of metastatic castration-sensitive prostate cancer. We also include a literature review of published cases of apalutamide-induced SCARs. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532009).

Case Presentation

An 83-year-old Caucasian male was diagnosed with metastatic castration-sensitive prostate cancer to the bone and lymph nodes. His prostate-specific antigen was 476.58 µg/L at diagnosis. He was commenced on the gonadotropin-releasing hormone receptor antagonist degarelix in order to suppress testosterone to castrate levels, with a 240 mg loading dose subcutaneously followed by 80 mg monthly thereafter. He then completed

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palliative radiotherapy to his thoracic and lumbar spine for pain management, 20 Gray in five fractions to both areas. Two months following diagnosis, he was commenced on apalutamide at a dose of 240 mg once daily continuously. His weight was 69.8 kg.

His past medical history was significant for polymyalgia rheumatica, osteoarthritis, and depression/anxiety. His past surgical history was significant for bilateral total knee replacements and a hernia repair. His regular medications included dexamethasone 4 mg once daily, pregabalin 50 mg twice daily, morphine sulphate 30 mg twice daily, paracetamol 1 g four times daily, sertraline 50 mg once daily, temazepam 10 mg nocte, pantoprazole 40 mg once daily, lactulose 15 mL twice daily, senna 15 mg twice daily, and ferrous fumarate 305 mg once daily. He had no known drug allergies. His Eastern Cooperative Oncology Group performance status was two at the time of commencement of apalutamide.

Five weeks after commencing apalutamide, the patient developed a vesicular zosteriform rash affecting his right T4 dermatome (see Fig. 1). He was commenced on valaciclovir at a dose of 1 g three times daily for management of presumed herpes zoster. Over the subsequent 3 days, the patient developed an erythematous maculopapular rash affecting his trunk. This progressed to involve his upper and lower limbs bilaterally, and he presented to his local emergency department for further management (see Fig. 2).

At that point, the rash was affecting approximately 80% of his body surface area (BSA). On the trunk, there was a widespread dusky red maculopapular eruption with areas of confluent erythema. There was evidence of skin detachment on the right mid back and blisters evolving on the anterior chest. There was widespread erythema and purpuric macules involving his bilateral arms and legs.

His bloodwork was mostly unremarkable, apart from a raised C-reactive protein at 61.1 mg/L and a mild normocytic anaemia of 10.0 g/dL. Eosinophil count was raised at 1.3×10^9/L. The following day, the patient was transferred to a tertiary centre for specialised dermatology and medical oncology input. He was reviewed by the dermatology team who felt the rash represented a severe cutaneous drug eruption presumed secondary to apalutamide. He was commenced on intravenous methylprednisolone at 2 mg/kg daily, as well as three-hourly paraffin gel topically. Apalutamide and all other non-essential medications were held.

Despite intravenous corticosteroids and regular paraffin gel application, his skin continued to deteriorate with the patient reporting severe pain. After 5 days in hospital, the rash had progressed to involve 95% BSA with a widespread dusky red macular eruption (see Fig. 3). Gentle rubbing of the skin resulted in skin detachment consistent with a positive Nikolsky sign. There were flaccid bullae involving the anterior chest and medial thighs bilaterally. There was also mucous membrane involvement of the anus with perianal skin detachment. Overall skin detachment was 12% of total BSA, including the area of presumed herpes zoster, consistent with SJS.

Skin biopsy of the left thigh was performed at this point which demonstrated skin with prominent interface change, basal vacuolation, and prominent dyskeratotic keratinocytes scattered throughout the epidermis (see Fig. 4). A superficial perivascular inflammatory infiltrate within the dermis containing lymphocytes and scattered eosinophils and neutrophils was also evident. These features were in keeping with SJS/TEN.

The rash deteriorated further with progressive skin detachment indicative of progression to overlap SJS/TEN. He was then commenced on intravenous immunoglobulin at 2 g/kg over 2 days, while continuing three-hourly paraffin gel. His SCORTEN score at this point was three, predicting a 35% risk of mortality. He was transferred to the intensive care unit (ICU) for 1:1 nursing care. He had a febrile episode associated with rigours on the same day, and so he was commenced on broad-spectrum intravenous antimicrobial cover. Wound swabs from his skin grew multiple organisms including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*.

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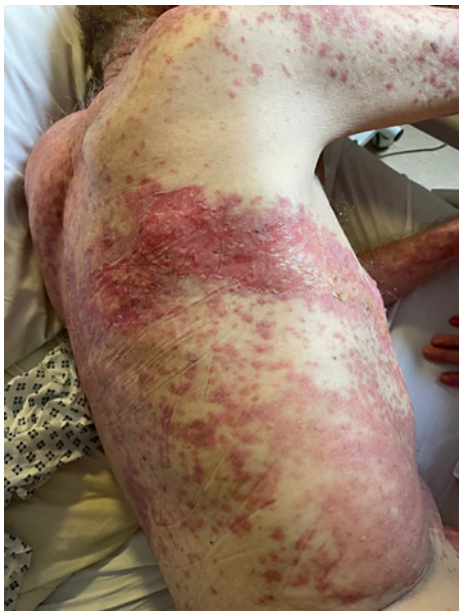

Fig. 1. Patient's back with zosteriform rash affecting right T4 dermatome and widespread erythematous maculopapular rash.

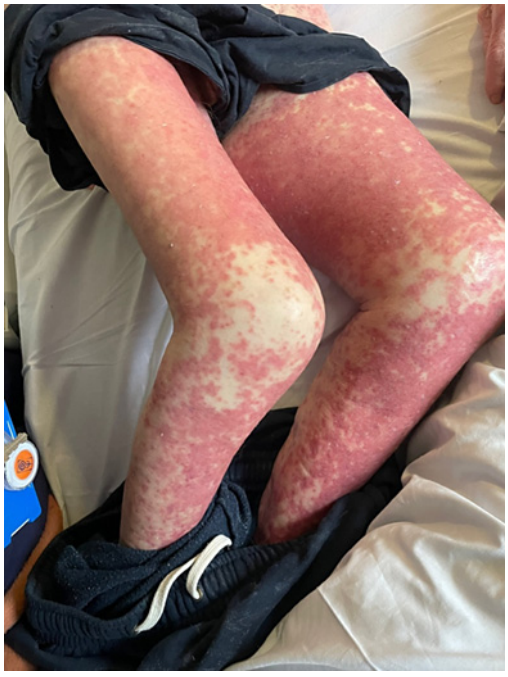

Fig. 2. Patient's lower limbs showing widespread erythema and purpuric macules.

Over the coming days, his skin gradually began to stabilise, and his corticosteroid dose was weaned. He was switched back to oral corticosteroids on day 21 after rash onset and back to his baseline dose of dexamethasone 4 mg once daily on day 23. He was transferred out of the ICU and back to the medical oncology ward on day 30, following 13 days in the ICU. Degarelix was restarted on day 36 without any recurrence of the skin rash. On day 38, he was transferred from the tertiary hospital back to his local hospital, however remained significantly deconditioned and off his baseline mobility (see Fig. 5 for timeline of events). Of note,

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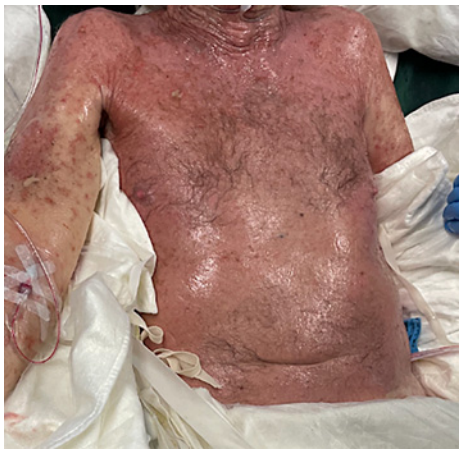

Fig. 3. Progression of rash despite intravenous methylprednisolone.

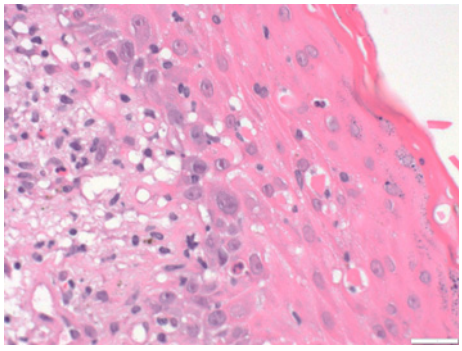

Fig. 4. Skin biopsy showing prominent interface change, basal vacuolation, and prominent dyskeratotic keratinocytes scattered throughout the epidermis with a superficial perivascular inflammatory infiltrate within the dermis.

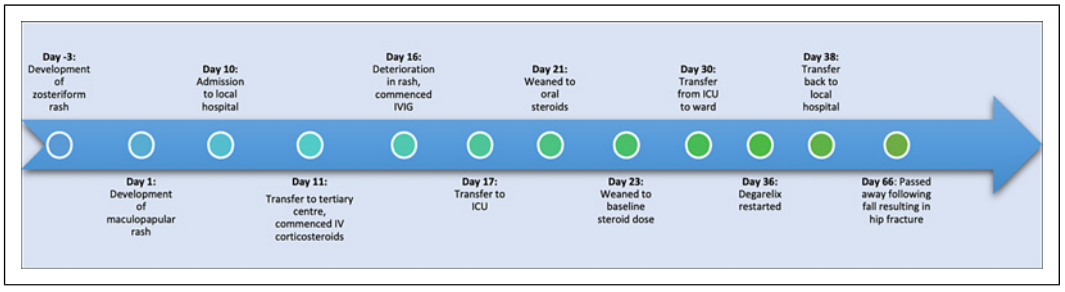

Fig. 5. Timeline of events.

his prostate-specific antigen had decreased from 476.58 μg/L at diagnosis to 28.6 μg/L at the time of discharge. He unfortunately passed away following a fall resulting in hip fracture 4 weeks post discharge.

Literature Review

Although there were no cases of DRESS or SJS/TEN reported in SPARTAN or TITAN, a number of cases of apalutamide-induced SCARs have been reported in the literature (see Table 1). Following a comprehensive literature review, we identified 9 reported cases of

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Table 1. Previously reported cases of apalutamide-induced SCARs

Reference	Clinical characteristics	Interval, weeks	Type of reaction	Severity	Histopathological features	Treatment	Outcome
[5]	77-year-old male Asian (Japanese)	2	TEN	SCORTEN 6	Full-thickness necrosis of the epidermis and mononuclear cell infiltration of the upper dermis	MP pulse therapy, IVIG	Died of multi-organ failure
[4]	83-year-old male Asian (Japanese)	6	TEN	SCORTEN 4	Multiple apoptotic keratinocytes with subepidermal bulla formation	MP pulse therapy, IVIG, plasmapheresis	Died of bacterial pneumonia
[6]	86-year-old male Asian (Japanese)	4	TEN	SCORTEN 2	Subepidermal blister with necrosis of individual epidermal cells	MP pulse therapy, IVIG, plasmapheresis	Recovered
[6]	91-year-old male Asian (Japanese)	10	TEN	SCORTEN 2	Interface dermatitis with necrosis of individual epidermal cells	MP pulse therapy, IVIG	Died of pneumocystis pneumonia
[7]	77-year-old male Asian (Japanese)	6	TEN	SCORTEN 4	Keratinocyte necrosis throughout the epidermis, subepidermal blistering	MP pulse therapy, IVIG, plasmapheresis, ciclosporin, and etanercept	Recovered
[9]	85-year-old male Asian (Taiwanese)	4	DRESS with possible SJS	N/A	Severe interface dermatitis with numerous apoptotic keratinocytes, whole layer epidermal necrosis, and dermal-epidermal separation. Perivascular lymphocyte infiltration, with abundant eosinophils and neutrophils, present in the dermis	MP	Recovered

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Table 1 (continued)

Reference	Clinical characteristics	Interval, weeks	Type of reaction	Severity	Histopathological features	Treatment	Outcome
[9]	77-year-old male Asian (Taiwanese)	5.5	DRESS with possible SJS	N/A	Severe interface dermatitis with confluent apoptotic keratinocytes, whole layer epidermal necrosis, and dermal-epidermal separation. Perivascular lymphocytes and eosinophil infiltration observed in the upper dermis	N/A	N/A
[10]	85-year-old male Caucasian	5.5	DRESS	N/A	Apoptotic keratinocytes and dermal infiltrate of eosinophils	Systemic steroids 0.5 mg/kg/day	Recovered
[8]	72-year-old male Asian (Japanese)	7	AGEP	N/A	Subcorneal and intraepidermal pustules admixed with many eosinophils	MP 60 mg, MP pulse therapy	Recovered

MP, methylprednisolone; IVIG, intravenous immunoglobulin; AGEP, acute generalised exanthematous pustulosis.

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apalutamide-induced SCARs. These include five cases of TEN [4–7], one case of acute generalised exanthematous pustulosis [8], and 3 cases of DRESS (two with possible overlapping SJS) [9, 10]. The median age of patients included in these cases is 83 years (range = 72–91 years). Eight of these nine cases (88.9%) involved Asian patients, with all reported cases of SJS/TEN occurring in Japanese patients. A subgroup analysis of Japanese patients included in the SPARTAN and TITAN trials identified that the incidence of skin rash in Japanese patients was nearly double the incidence in the global populations of both studies. Rash occurred in 56% of Japanese patients in SPARTAN compared to 23.8% of the global population, while rash occurred in 50% of Japanese patients in TITAN compared to 27.1% of the global population [11].

All patients with apalutamide-induced TEN were treated with methylprednisolone therapy initially, and 100% of patients ultimately required additional immunosuppressive therapy. All 5 patients received intravenous immunoglobulin, with three also undergoing plasmapheresis. All patients who received plasmapheresis had improvement of rash initially, although 1 patient ultimately died of bacterial pneumonia, and another had recurrence of rash requiring ciclosporin and etanercept [4, 6, 7]. Apalutamide has a long half-life of 110–231 h as it is highly protein-bound in serum [12]. This might suggest why plasmapheresis could be particularly effective for apalutamide-induced TEN. Three of five reported cases of apalutamide-induced TEN (60%) ultimately resulted in death.

The median time to onset of skin rash was 82 days in SPARTAN and 81 days in TITAN; however, the majority of rashes reported in these trials were of low grade [2, 3]. Our review identified that apalutamide-induced SCARs typically have a shorter time to onset, with a median time to onset of 39 days (range = 14–70 days). Therefore, an early time to onset of skin rash following commencement of apalutamide may potentially be indicative of a more severe reaction. Similarly, in our case, time to rash onset was shorter than reported in the trials at 35 days.

The mechanism of apalutamide-induced skin rash is poorly understood. Apalutamide results in higher incidence of skin rash compared to other antiandrogens used for treatment of prostate cancer [13]. Ji et al. [13] have hypothesised that the 2-cyanopyridine moiety present in apalutamide can react with cysteine residues in proteins, producing hapten that may trigger immune responses which in turn may lead to development of skin rash. Japanese race is clearly a risk factor for skin rash as previously mentioned [11]. A subgroup analysis of the SPARTAN trial demonstrated that baseline characteristics of the Japanese cohort were consistent with those of the global population, except for body weight. Body weight was significantly lower in the Japanese subgroup with a median weight of 61.9 kg (range = 46–84 kg) compared to 85 kg (range = 45–182 kg) [14]. Additionally, a multicentre, retrospective study of Japanese patients receiving apalutamide aimed to assess the impact of body weight on skin-related adverse events. This found that patients with a body weight of less than 67 kg and a body mass index of less than 24 kg/m^2 had significantly higher rates of skin toxicity [15].

Conclusions

SJS and TEN are variants of the same condition involving skin detachment and mucosal loss and are associated with significant mortality rates. We report a case of apalutamide-induced SJS/TEN in a patient receiving apalutamide combined with degarelix for the treatment of metastatic castration-sensitive prostate cancer. We discuss other reported cases of SCARs associated with apalutamide, with the majority of these occurring in Asian patients. Low body weight and Japanese race seem to be risk factors for apalutamide-induced SCARs, as

well as short time to onset of skin rash. In this case, time to rash onset was shorter than reported in clinical trials at 35 days; however, there were no clinical risk factors for skin toxicity as far as we are aware. To our knowledge, this is the first reported case of apalutamide-induced overlap SJS/TEN in Europe or in a Caucasian patient. It is therefore likely to be a very rare toxicity. Although the temporal relationship between the development of skin rash and commencement of apalutamide is very suggestive of causation, it is possible that it was unrelated to apalutamide. More real-world data is required to assess the frequency of this toxicity. It is important that patients are educated about this important adverse event, and that skin rashes are managed early to avoid development of SCARs such as SJS/TEN which are associated with a high mortality.

Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images prior to their passing away.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding is required for this study.

Author Contributions

Calvin R. Flynn: conceptualization, methodology, writing – original draft preparation, and investigation. Shun-Chieh Liu: writing – original draft preparation. Berbie Byrne, James Ralph, Gabriela Paz, Salman Anwar, Jemma Buchalter, Orla M. Fitzpatrick, and Trevor Markham: writing – reviewing and editing. Paul Donnellan: supervision.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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