

Maculopapular Drug Eruption Caused by Apalutamide: Case Report and Review of the Literature

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Apalutamide, an oral androgen receptor signaling inhibitor, is approved for the treatment of non-metastatic castration-resistant prostate cancer and metastatic prostate cancer. In the international randomized placebo-controlled clinical trials, apalutamide was associated with a higher rate of rash than placebo. However, given that reports from a dermatological perspective are limited, the skin manifestations and histopathology of the skin lesions caused by apalutamide are largely unknown. Here, we report a case of apalutamide-induced drug eruption. A 66-year-old man developed itchy maculopapular erythema on the trunk and extremities 10 weeks after starting apalutamide for progressive prostate cancer. A biopsy specimen showed interface dermatitis with perivascular lymphocytic infiltration in the upper dermis. The lymphocyte transformation test was positive for apalutamide. The skin manifestations improved after discontinuation of apalutamide and treatment with topical corticosteroids and systemic prednisolone. A review of the dermatology literature on apalutamide-induced drug eruption yielded only six cases, including our case. Dermatologically, there were four cases of maculopapular rash and two of toxic epidermal necrolysis and histopathologically, there were three cases of interface dermatitis, two of epidermal necrosis, and one of spongiotic dermatitis. Four patients had peripheral eosinophilia. A lymphocyte transformation test was performed in three cases and was positive for apalutamide in all cases. Except for the two cases of toxic epidermal necrolysis, which were fatal, the skin eruptions appeared 10 weeks after starting apalutamide. Considering the increasing number of patients with prostate cancer being treated with apalutamide, cases of apalutamide-induced drug eruption need to be accumulated and analyzed. (*J Nippon Med Sch* 2022; 89: 550–554)

Key words: drug eruption, apalutamide, prostate cancer, maculopapular rash, interface dermatitis

Introduction

Apalutamide, an oral selective androgen receptor (AR) inhibitor, prevents nuclear translocation of the AR and AR-mediated transcription by directly binding to the AR, resulting in inhibition of growth of prostate cancer cells¹. Apalutamide is approved by the US Food Drug Administration for the treatment of non-metastatic castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer based on data from two international, randomized, placebo-controlled Phase III trials, namely, SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) and TITAN (Targeted Investiga-

tional Treatment Analysis of Novel Anti-androgen)^{2,3}. In Japan, apalutamide has been approved for the treatment of non-metastatic castration-resistant prostate cancer and metastatic prostate cancer since 2019.

The incidence of skin rash was found to be higher in the apalutamide group than in the placebo group in both SPARTAN (23.8% vs. 5.5%) and TITAN (27.1% vs. 8.5%)^{2,3}. Notably, a subgroup analysis of Japanese patients in both studies revealed that apalutamide-induced skin rash was more prevalent in the Japanese population than in the global population (56.0% vs. 0.0% in SPARTAN and 50.0% vs. 8.7% in TITAN)⁴.

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However, in both these studies, a wide variety of exanthemata was observed in patients treated with apalutamide, including maculopapular rash, butterfly rash, erythematous rash, generalized rash, papules, pruritic rash, pustular rash, lupus rash, erythema multiforme, stomatitis, and urticaria, which were grouped together as “rash”^{2,3}. Thus, the details of the skin manifestations in each case and the histopathology of the skin lesions caused by apalutamide are largely unknown. Moreover, given the lack of data on the results of the lymphocyte transformation test (LTT) and/or the patch test for apalutamide in these clinical trials, the possibility that the skin rash was caused by other medication (s) taken concomitantly with apalutamide cannot be ruled out. Therefore, reports from a dermatological perspective would be helpful for a better understanding of apalutamide-induced skin reactions. Here, we report a case of maculopapular drug eruption caused by apalutamide and review the literature on apalutamide-induced drug eruptions from a dermatology perspective.

Case Report

A 66-year-old man was diagnosed to have prostate cancer with bone metastases (cT3N1M1b) and treated with cabazitaxel plus denosumab therapy, enzalutamide 160 mg/day, and abiraterone acetate 1,000 mg/day. However, his disease was recalcitrant to these therapies and progressive, indicated by an increasing serum prostate-specific antigen (PSA) level. Therefore, apalutamide 240 mg/day was started. His medical history included hypertension and thalamic hemorrhage, which were treated with olmesartan medoxomil, trichlormethiazide, and nifedipine. These medications had been administered for several years without any dose changes.

Ten weeks after starting apalutamide, the patient presented with extremely itchy eruptions over his entire body. It was difficult to distinguish a drug eruption from viral exanthema at the initial presentation, and topical corticosteroids and antihistamines were administered without ceasing any of his other medications. However, 3 days later, the patient re-presented with worsening skin eruptions. Physical examination revealed infiltrated erythema on the posterior of the auricle (**Fig. 1A**), diffusely distributed erythema on the chest and abdomen (**Fig. 1B**) and a confluent infiltrated erythematous rash on the back (**Fig. 1C**), arms, and legs (**Fig. 1D**) that were affecting nearly 80% of his body. He complained of fatigue and was barely able to maintain a standing position. He had no fever, mucosal involvement, or lymphadenopathy.

Laboratory investigations revealed peripheral eosinophilia (1547/ μ L, normal range <500/ μ L) and slightly increased levels of lactate dehydrogenase (295 IU/mL, normal range 124-222 IU/mL) and C-reactive protein (0.59 mg/mL, normal range <0.14 mg/mL) but were otherwise normal.

A biopsy specimen from an erythematous area on the left thigh revealed interface dermatitis consisting of parakeratosis, exocytosis of lymphocytes, partial spongiosis in the epidermis (**Fig. 2A**), and vacuolar degeneration of the dermo-epidermal junction with perivascular infiltration of lymphocytes in the upper dermis, and few apoptotic cells in the epidermis (**Fig. 2B**). The Naranjo adverse drug reaction probability scale score for apalutamide was 6 whereas that for other medications was 0, indicating that apalutamide was the “probable” cause of the drug eruption⁵. Moreover, the LTT was positive for apalutamide (stimulation index 235%, normal range <180%). Based on these clinical, laboratory, and histopathological findings, we concluded that apalutamide was the culprit drug in this case.

Apalutamide was discontinued, and the patient was treated with topical corticosteroids and oral prednisolone 30 mg/day. Expansion of the skin eruptions stopped 3 days after starting prednisolone, and the itching and erythema disappeared within 2 weeks. His other medications have been continued and he has been no recurrence of skin rash. He is now stable with administering docetaxel (120 mg) every three weeks.

Discussion

We have encountered a case of maculopapular drug eruption that was found to be interface dermatitis on histopathological examination and caused by administration of apalutamide. Although skin rashes were frequently observed in patients treated with apalutamide in the clinical trials, there have been no detailed reports on apalutamide-induced drug eruption from a dermatological perspective. To the best of our knowledge, there have been only four reports of apalutamide-induced drug eruption in the field of dermatology, three of which were published in English⁶⁻⁸ and one in Japanese⁹, and all were from Japan. **Table 1** summarizes the six prostate cancer cases of apalutamide-induced drug eruption, including our own. Two cases were patients with fatal toxic epidermal necrolysis (TEN)^{6,7}, one of whom had high levels of SS-A antibodies, indicating an autoimmune cause⁶, and the other had thrombocytopenia due to myelodysplastic syndrome⁷. The presence of malignancy is included

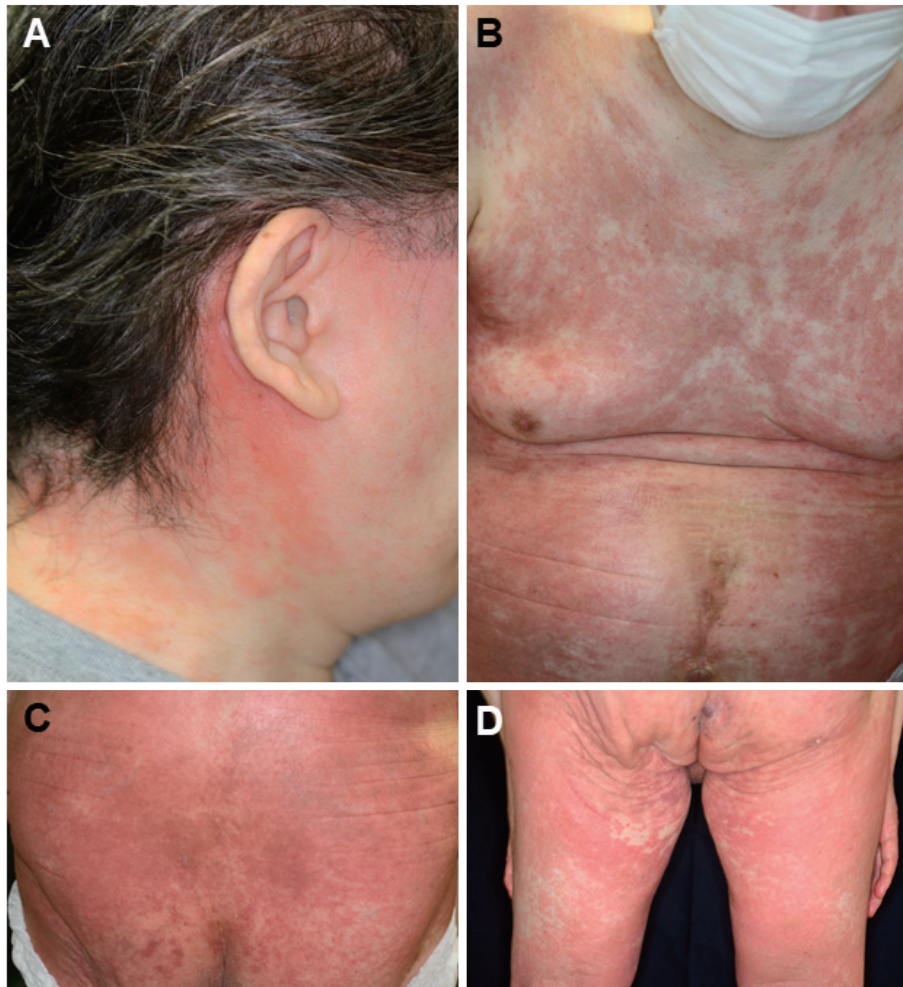


Fig. 1 Clinical manifestations at the second presentation. (A) Itchy infiltrated erythema on the posterior of the auricle. (B) Diffusely distributed erythema on the chest and abdomen. Erythema was confluent on the back (C) and legs (D).

among the risk factors for TEN in the SCORTEN (Severity-of-Illness Score For Toxic Epidermal Necrolysis) system¹⁰.

One of the characteristics of apalutamide-induced drug eruption is a relatively long time interval from the start of treatment with apalutamide to the onset of rash. It has been reported that the median time to appearance of skin rash is 82 days after starting apalutamide². However, in cases of TEN, the time interval appears to be shorter (2-6 weeks) than in other cases (average 10 weeks; **Table 1**). Therefore, early onset of skin rash in patients with apalutamide may be a sign of severe disease. Eosinophilia was reported in four of the six cases. LTT was performed in three cases, and apalutamide was positive on all occasions.

Except for the TEN cases (cases 1 and 2), in which full-thickness epidermal necrosis was found^{6,7}, the skin lesions were histopathologically characterized as interface dermatitis (cases 3, 4, and 6)⁹ or spongiotic dermatitis

(case 5; **Table 1**)⁸. In cases 3 and 4, parakeratosis, exocytosis of lymphocytes, and apoptotic keratinocytes were observed in the epidermis with inflammatory cells infiltrating the upper dermis in a lichenoid pattern⁹. In case 5, spongiotic dermatitis with exocytosis of lymphocytes and perivascular infiltration of lymphocytes and eosinophils in the upper dermis were observed. Apoptotic cells were rarely detected in our case and in case 5. The presence or absence of apoptotic cells varied from case to case. In graft-versus-host disease, the number of epidermal apoptotic cells determines the severity of the disease¹¹. Therefore, skin biopsy can be an important tool for assessing the severity of disease.

In general, drug eruptions require discontinuation of the suspected culprit drug. However, apalutamide was discontinued in only 9.9% of patients who developed skin rash in SPARTAN and in only 8.5% in TITAN^{2,3}. In most cases, the skin rash was treated with topical corticosteroids, antihistamines, and systemic corticosteroids

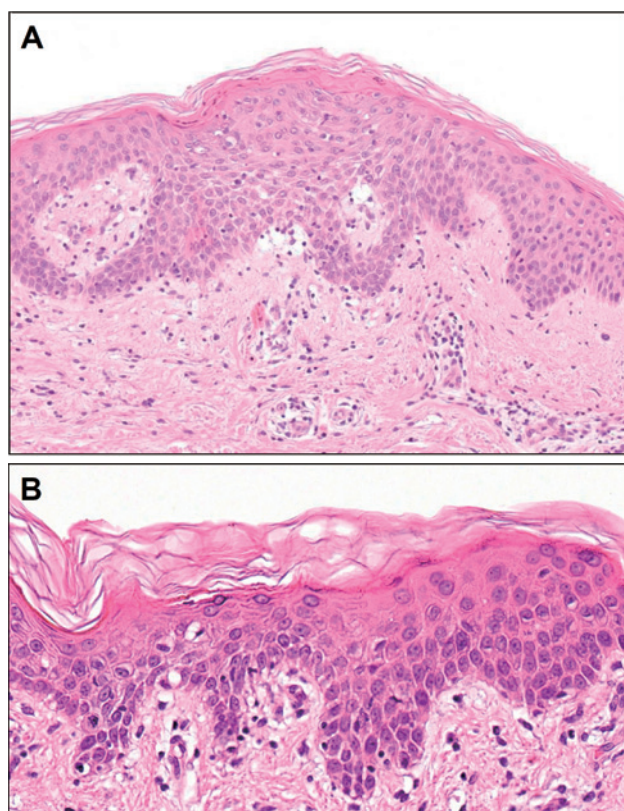


Fig. 2 Histopathological findings in a specimen obtained from an erythematous area on the left thigh. (A) Interface dermatitis consisting of parakeratosis, exocytosis of lymphocytes, partial spongiosis in the epidermis (HE staining, ×200). (B) Vacuolar degeneration at the dermo-epidermal junction. Most of the infiltrated inflammatory cells were lymphocytes. Apoptotic cells were rarely observed (HE staining, ×400). HE, hematoxylin and eosin.

with only interruption of treatment with apalutamide or a reduction of the dose. The fact that these patients could be treated by dose reduction suggests that apalutamide-induced drug eruptions occur in a dose-dependent manner. In our case, apalutamide was discontinued because the PSA level remained elevated even after apalutamide was introduced; however, if apalutamide is effective in the treatment of prostate cancer, it may be worthwhile considering dose reduction first. In case 5, there was no recurrence of skin rash when apalutamide was continued at half the dose with addition of prednisolone⁸.

Our patient had not developed any skin problems when on enzalutamide before apalutamide. Clinical trials have shown that the rate of skin rash in patients on enzalutamide is similar to that in those on placebo. Structural differences may account for the difference in frequency of rash between apalutamide and enzalutamide¹². The 2-cyanophenyl and dimethyl moieties in enzalutamide are substituted in apalutamide with 2-cyanopyridine and cyclobutyl, respectively (Fig. 3). The 2-cyanopyridine moiety may react with cysteine residues in serum proteins to form haptens, triggering an immune response and increasing the potential for skin rash.

Are there any risk factors that predispose to drug eruptions caused by apalutamide? A number of clinical risk factors, including Eastern Cooperative Oncology Group Performance Status, baseline PSA, time from diagnosis to first dose, Gleason score, and previous treatment have been considered, but no definite risk factors have been found⁴. The exact reason why the incidence of drug eruption for apalutamide is higher in Japanese is un-

Table 1 Prostate cancer case reports of apalutamide-induced drug eruption

Case	Age	Skin manifestation	CTCAE	Interval*	Eosinophilia	Histopathology	LTT	Treatment	Outcome	Reference
1	77	TEN	Grade 5	2 w	None	epidermal necrosis	+	mPSL pulse therapy, IVIG	dead	6
2	83	TEN	Grade 5	6 w	n.d.	epidermal necrosis	+	mPSL pulse therapy, IVIG plasmaphoresis	dead	7
3	80s	Maculopapular	Grade 2	11 w	+	interface dermatitis	n.d.	topical corticosteroids	resolved	9
4	70s	Maculopapular	Grade 2	9 w	+	interface dermatitis	n.d.	topical corticosteroids	resolved	9
5	78	Maculopapular	Grade 3	10 w	+	spongiotic dermatitis	n.d.	dose reduction, systemic PSL	resolved	8
6	6	Maculopapular	Grade 3	10 w	+	interface dermatitis	+	topical corticosteroids systemic PSL	resolved	this case

CTCAE, Common Terminology Criteria for Adverse Events; IVIG, intravenous immunoglobulin therapy; LTT, lymphocyte transformation test; mPSL, methylprednisolone; n.d., not described; PSL, prednisolone; TEN, toxic epidermal necrolysis; w, weeks.

*Interval indicated the period from the start of treatment with apalutamide to the onset of rash.

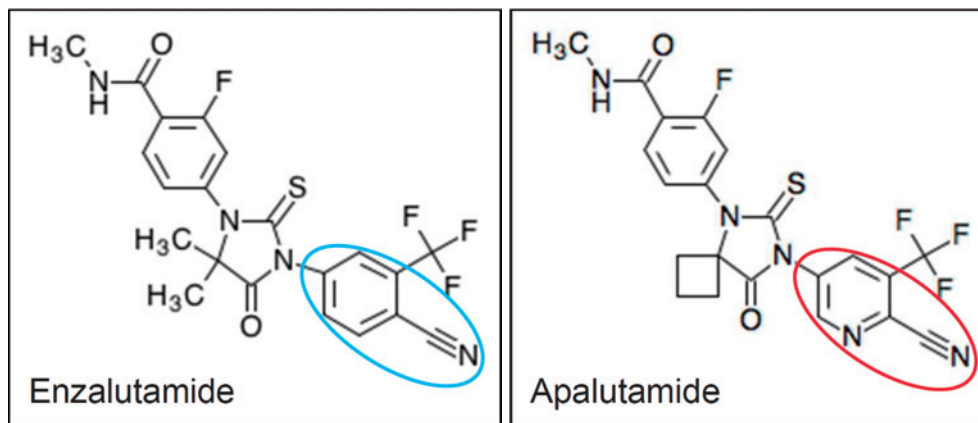


Fig. 3 Chemical structures of enzalutamide and apalutamide. The 2-cyanophenyl (blue) and 2-cyanopyridine (red) moieties are indicated. The structures are reproduced with the permission of the Kyoto Encyclopedia of Genes and Genomes (KEGG) Drug database.

known. Since in the international phase III clinical trials, the same amount of apalutamide was used regardless of race, the higher dose of apalutamide per body weight was associated with a higher incidence in Japanese⁴⁹.

In summary, although apalutamide-induced drug eruption affects a large area of skin, the skin manifestations are easily treated in most cases. However, it should be noted that this type of eruption can be fatal, depending on the underlying disease, such as malignancy and autoimmune disease. The presence or absence of epidermal cell necrosis is useful for predicting the severity of the eruption, the choice of treatment, and the prognosis.

Conflict of Interest: None.

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