SHORT COMMUNICATION

# Toxic Epidermal Necrolysis Caused by Apalutamide: A Case Report of Treatment Using Etanercept with Conventional Steroid Therapy

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Apalutamide is an androgen receptor inhibitor used for treatment of prostate cancer. It occasionally causes severe cutaneous disorders, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (1–3). We report here a case of TEN caused by apalutamide, which was treated successfully using etanercept with conventional therapies.

## CASE REPORT

A Japanese man in his 70s received 240 mg/day of apalutamide for metastatic prostate cancer. He developed fever and erythema across his entire body 43 days after initiating apalutamide, and his erythema was associated with subsequent erosions (**Fig. 1**A). Although apalutamide was terminated, erosions with blood crusts developed on his lips and oral mucosa (Fig. 1B). Skin biopsy of the erythema revealed keratinocyte necrosis throughout the epidermis, associated with subepidermal blistering (Fig. 1C). Based on the clinical and histopathological findings, a diagnosis of TEN was made. Severity-of-illness score for TEN was 4 on the first day of admission. Pulse therapy was started using 1,000 mg methylprednisolone (mPSL); however, fever and erosions in the oral cavity relapsed after completion of the pulse therapy. Subsequently, intravenous immunoglobulin (IVIG), 400 mg/kg daily, was administered for 5 days. As the symptoms occurred repeatedly, the patient was treated with mPSL pulse therapy again, and plasmapheresis twice, followed by administration of ciclosporin. However, the same symptoms developed on day 33 and day 50, and etanercept, (50 mg once a week) was initiated. Subsequently, all symptoms disappeared after 6 doses of etanercept. While tapering oral prednisolone and ciclosporin, the patient repeatedly developed erythema, which resolved on increasing the dose of ciclosporin. Prednisolone was terminated after 8 months, and ciclosporin is still being tapered. The drug-induced lymphocyte stimulation test was positive for apalutamide (stimulation index, 263%).

## DISCUSSION

In clinical trials the incidence of adverse skin events due to apalutamide was nearly double in the Japanese population compared with the global population (4). To date, 4 cases of TEN caused by this agent have been reported (1–3) (**Table I**). Although all 4 cases were Japanese, further investigations are required to elucidate the differences in incidence among races. It should be noted

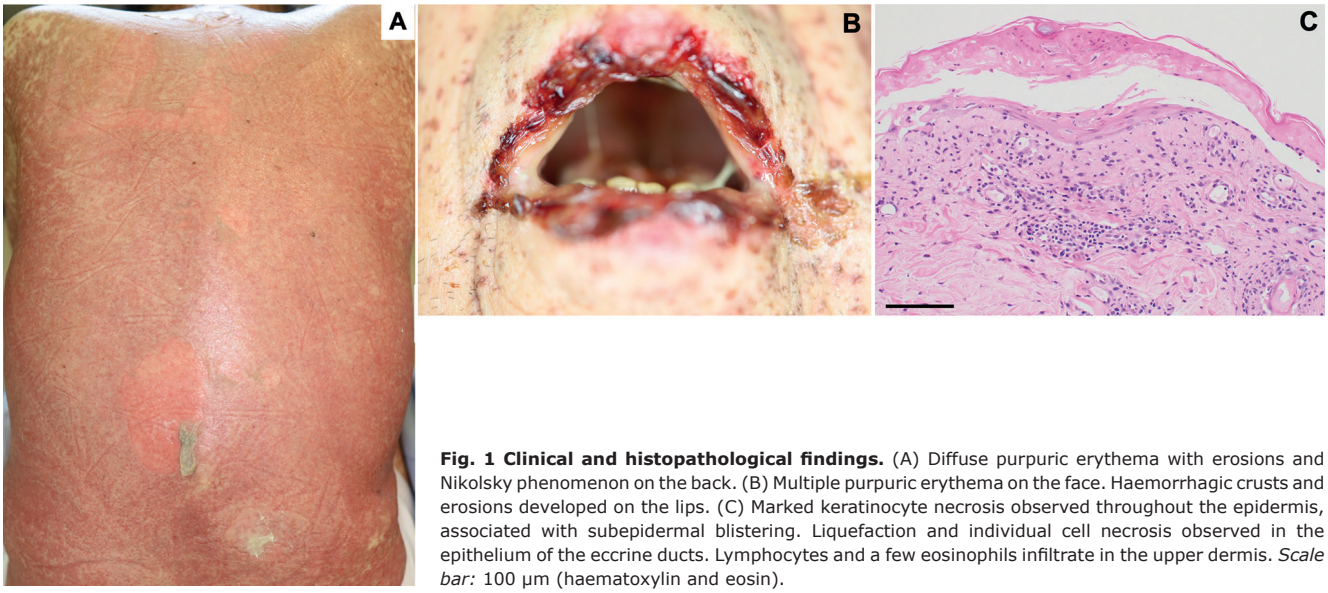


**Fig. 1 Clinical and histopathological findings.** (A) Diffuse purpuric erythema with erosions and Nikolsky phenomenon on the back. (B) Multiple purpuric erythema on the face. Haemorrhagic crusts and erosions developed on the lips. (C) Marked keratinocyte necrosis observed throughout the epidermis, associated with subepidermal blistering. Liquefaction and individual cell necrosis observed in the epithelium of the eccrine ducts. Lymphocytes and a few eosinophils infiltrate in the upper dermis. *Scale bar:* 100 μm (haematoxylin and eosin).

**Table I. Summary of reported cases of toxic epidermal necrolysis caused by apalutamide**

| Case | Age, years | Onset | SCORTEN | Treatment | Outcome | Reference number |
|---|---|---|---|---|---|---|
| 1 | 83 | 6 weeks | 4 | mPSL pulse therapy, IVIG, plasmapheresis | Died[a] | 1 |
| 2 | 77 | 2 weeks | 6 | mPSL pulse therapy, IVIG, | Died[b] | 2 |
| 3 | 86 | 4 weeks | 2 | mPSL pulse therapy, IVIG, plasmapheresis | Alive | 3 |
| 4 | 91 | 2.5 months | 2 | mPSL pulse therapy, IVIG | Died[c] | 3 |
| 5 | 77 | 43 days | 4 | mPSL pulse therapy, IVIG, plasmapheresis, ciclosporin, etanercept | Alive | Current case |

Cause of death: [a]bacterial pneumonia; [b]multi-organ failure; [c]pneumocystis pneumonia.
Onset: time to onset after initiating apalutamide; SCORTEN: severity-of-illness score for toxic epidermal necrolysis; mPSL: methylprednisolone; IVIG: intravenous immunoglobulin.

that 3 of the cases were fatal, and this drug should be recognized as a causative agent of severe drug eruptions. The current case was treated by intensive therapeutic interventions, but there were repeated relapses. One possible mechanism of relapse is the slow pharmacokinetics of apalutamide (1). In addition, individual differences in drug metabolism may influence the prolonged skin inflammation.

To treat SJS/TEN, systemic therapies are generally used, mainly corticosteroids, mPSL pulse therapy, IVIG, ciclosporin, plasmapheresis, and their combinations. In the aforementioned fatal cases, the patients were treated with mPSL pulse therapy, IVIG, and/or plasmapheresis; however, the treatments failed. Recently, blockade of tumour necrosis factor (TNF)-α has attracted attention as a novel intervention for SJS/TEN, which can shorten the re-epithelization time (5). Among anti-TNF-α agents, etanercept is most commonly used and effective for SJS/TEN patients. Etanercept has a shorter half-life than infliximab and adalimumab (6). In addition, anti-TNF-α agents have been rarely reported to worsen solid tumours. Therefore, temporary use for cancer-bearing patients may be acceptable. The current case also demonstrated the efficacy and safety of using etanercept with conventional interventions to treat SJS/TEN due to apalutamide.

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*The authors have no conflicts of interest to declare.*

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