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LETTER TO THE EDITOR

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WILEY

A case of toxic epidermal necrolysis associated with apalutamide administration

Dear Editor,

Apalutamide, a novel nonsteroidal antiandrogen agent, is used for the treatment of castration-resistant prostate cancer. Although skin rash is a common side effect of apalutamide, toxic epidermal necrolysis (TEN) has not been reported yet. Here, we report a case of apalutamide-associated TEN.

A 77-year-old male patient received apalutamide (240 mg/day) for the treatment of prostate cancer, metastasized to bladder and rectum. Two weeks after initiating apalutamide, he experienced fatigue and erythema on his trunk. He continued apalutamide and visited our hospital 12 days after the onset of rash. Physical examination revealed high fever and erythema, with atypical target lesions on trunk and skin detachment over 30% of the body surface area. Hemorrhagic erosions on the lips, oral mucosa, and genital region were also observed. Nikolsky's sign was positive. Ophthalmological examination showed severe dry eyes. No leukocytosis or eosinophilia was observed. Laboratory testing revealed liver and renal dysfunction and high anti-SS-A antibody titer (1810 U/mL), in the absence of elevated antinuclear and anti-SS-B antibody titers. Histological examination showed full-thickness necrosis of the epidermis and mononuclear cell infiltration of the upper dermis (Figure 1A,B). Thus, we diagnosed TEN and all medications including apalutamide, lubiprostone, magnesium oxide, irbesartan, febuxostat, linagliptin, vonoprazan fumarate, and apixaban were discontinued.

The patient's severity-of-illness score for TEN (SCORTEN)[1] was 6. He was placed on mechanical ventilation for unstable hemodynamics in

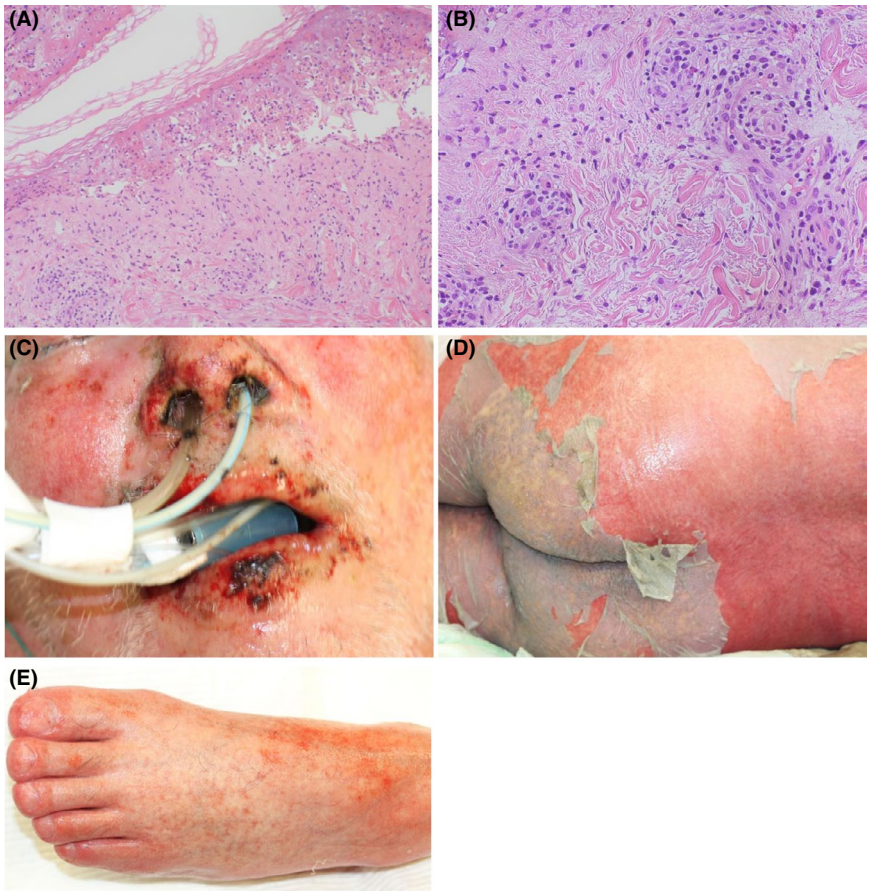

FIGURE 1 A, Histological findings from the forearms: full-thickness epidermal necrosis and subepidermal bulla. B, Inflammatory lymphocyte infiltration of the dermis. Hematoxylin and eosin staining. Magnification 200× (A) and 400× (B). (C) Clinical presentation of the patient. Erosions on the nose, lips, and oral mucosa. (D) Widespread epidermal loss on the trunk. (E) All toenails were removed

the intensive care unit. Methylprednisolone pulse therapy (1000 mg/day, 3 days) and intravenous immunoglobulin therapy (400 mg/kg/day, 5 days) were administered. However, skin detachment rapidly progressed over his entire body (Figure 1C–E). During treatment, multiple lymph nodes and adrenal gland metastases appeared. On day 53 from the onset, he died due to multi-organ failure.

Comparison of the Naranjo Adverse Drug Reaction Probability Scale[2] scores of apalutamide (5) and other concomitant medicines (0) indicated apalutamide as a probable cause of TEN. The lymphocyte transformation test was positive for apalutamide (stimulation index: 1.96), suggesting apalutamide as the culprit drug. The high anti-SS-A antibody titer and severe dry eyes suggested Sjögren's syndrome or another autoimmune disease, although no other autoimmune symptoms were observed. Patients with Sjögren's syndrome have higher rates of drug allergies than healthy individuals[3], and autoimmune factors may facilitate the development of TEN.

In the APR-509 phase 3 trial, rash occurred in 23.8% of patients (Grade 3/4 in 5.2%),[4] with a median appearance 82 days after starting apalutamide. Compared to enzalutamide, another androgen receptor inhibitor, apalutamide resulted in a higher incidence of rash. Ji et al[5] hypothesized that the 2-cyanopyridine moiety in apalutamide may react with cysteine residues in proteins to form haptens, which may trigger immune responses and lead to the development of rashes. Notably, the incidence of rash is higher in the Japanese population (19/34; 55.9%).[6] Although the reason is unknown, it may be related to the high dose of the drug per body weight in Japanese or some possible genetic differences.

In conclusion, continued apalutamide administration after the onset of rash and tumor progression may have resulted in intractable TEN. Considering the recent approval of apalutamide, careful observation is needed to detect adverse cutaneous events, especially in patients with autoimmune disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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KEYWORDS

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