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CASE REPORT

Severe type of erythema multiforme (EM major) due to administration of Anti-PD-1 antibody drug

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ABSTRACT

Immune checkpoint inhibitors can sometimes cause unexpected skin side effects. Special attention should be paid to a severe form of erythema multiforme (EM), toxic epidermal necrolysis and Stevens-Johnson syndrome. We experienced a patient who took 10 weeks from drug discontinuation to the onset of EM major.

Keywords: Immune Checkpoint Inhibitors; Immune-related Adverse Events; Erythema Multiforme; Erythema Multiforme Major

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1. Introduction

Immune checkpoint inhibitors (ICI) have radically changed the treatment of several cancers[1]. Of note, in addition to an increased anti-tumor immunity, the mechanism of action of ICIs reveals a new toxicity profile called immune-related adverse events (irAEs)[2,3]. All organs can be affected by these new toxicities, although the more frefrequently affected organs include the skin, digestive, and endocrine or- gans[3,4]. The majority of toxicities caused by ICIs are low in severity, but some are more serious and require multidisciplinary management of side effects[5]. In the case of skin, a severe form of erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome are very serious, and diagnosis and treatment are frequently difficult. Recently we encountered a case with a severe type of erythema multiforme (EM major) due to administration of anti-PD-1 antibody drug, who showed a unique clinical course. Herein this case is reported.

2. Case presentation

Two years before the first visit to our department, an 80-year-old Japanese man had been aware of fatigue and shortness of breath during exertion, and visited the department of respiratory medicine in Takatsuki Red Cross Hospital, Osaka, Japan. His past history included chronic obstructive pulmonary diseases and type II diabetes. Upon closer examination, he was diagnosed as lung adenocarcinoma stage IV (multiple metastases in lymph nodes, multiple rib and iliac). Chemotherapy with carboplatin and pemetrexed was started, and one year before the first visit, the improvement of lung, multiple lymph nodes, and multiple rib/iliac metastases was observed, but renal function was

deteriorated, so the procedure was completed in 5 courses. Six months later, metastasis progressed, and an anti-PD-1 antibody drug (pembrolizumab) was administered. Pembrolizumab was discontinued after 6 courses due to drug-induced lung disorder. The administration of pembrolizumab was discontinued and the patient was followed up, but 10 weeks after the discontinuation of the administration, erythematous lesions with pruritus appeared on the face and neck. Topical corticosteroids were used, but the skin lesions spread throughout the body 2 days later, and he was refered to our department for detailed examination and treatment.

At the first visit, body temperature was 37°C and there was no hyperemia in the bulbar conjunctiva. He had erosive lesions on lips. Coin-sized erythema was scattered on the face, auricle, and neck (**Figure 1**). The back of the abdomen and limbs were scattered with coin-sized erythema with the infiltration, and some of them tended to heal. Fused atypical erythematous lesions were seen throughout the body (**Figure 2**).

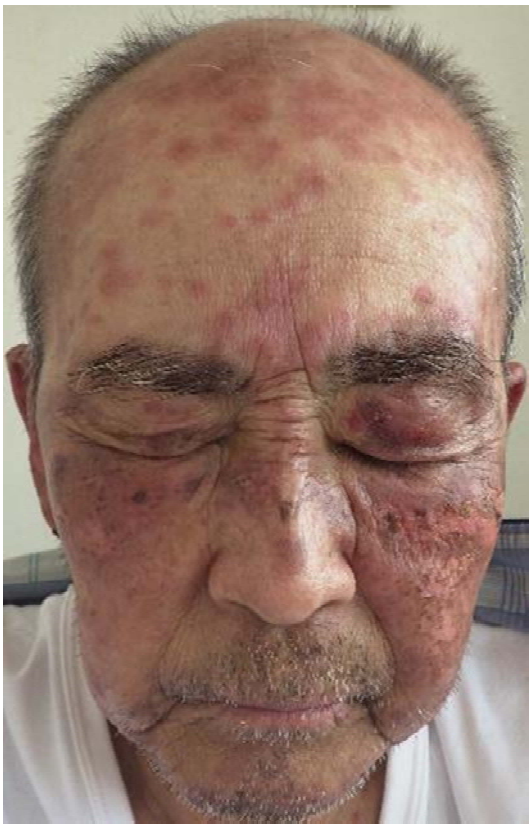

Figure 1. The patient had erosive lesions on lips, and coin-sized erythema was scattered on the face, auricle, and neck**.**

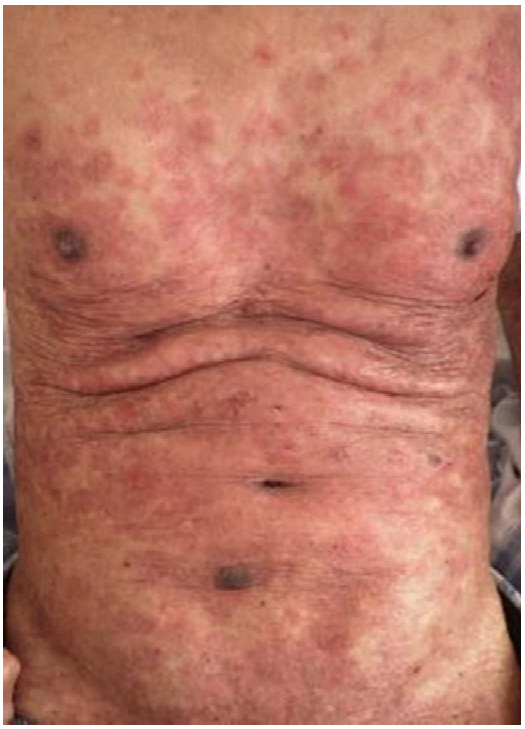

Figure 2. Coin-sized erythematous lesions with the infiltration and fused atypical lesions were seen throughout the body**.**

Blood test findings at the first visit. No increase in eosinophils or liver enzymes was observed. Considering the possibility of bullous pemphigoid and pemphigus vulgaris, anti-desmoglein antibodies and anti-BP180 antibody were measured, but they were within the standard values.

A skin biopsy, it was obtained from the abdominal lesion. There are vacuolar degeneration and individual cell necrosis at the epidermal-dermis junction. Infiltration of inflammatory cells (mainly lymphocytes) around the superficial blood vessels of the dermis (**Figure 3**).

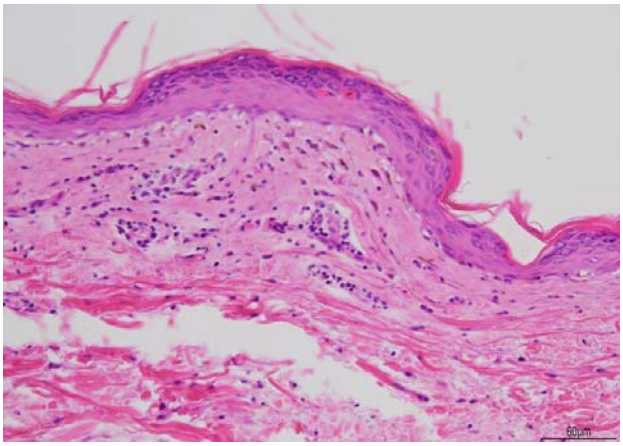

Figure 3. Pathological findings revealed vacuolar degeneration and individual cell necrosis at the epidermal-dermis junction (x200)**.**

Possibility of drug eruption other than pem-

brolizumab was considered and the possible drugs that caused EM major were discontinued. Although PSL was 0.5 mg/kg/day was administered, the skin lesions expanded. Based on the pathological finding and clinical lesions such as the increased severity, erythematous lesions located in the extremities and mild mucosal lesions, we diagnosed EM major.

Due to drug-induced lung injury, 6 cools pembrolizumab were completed and 10 weeks had passed. Initially, considering drug eruption other than pembrolizumab, possible agents discontinued such as magnesium oxide tablets, eszopiclone, lansoprazole enteric coated tablets, sulfamethoxazole/trimethoprim tablets, and PSL 0.5 mg / kg started. However, the eruption expanded and erosion of the lips also appeared. Considering irAEs of pembrolizumab, the dose was increased to 1 mg/kg of PSL, and the eruption was improved and the PSL was gradually decreased (**Figure 4**).

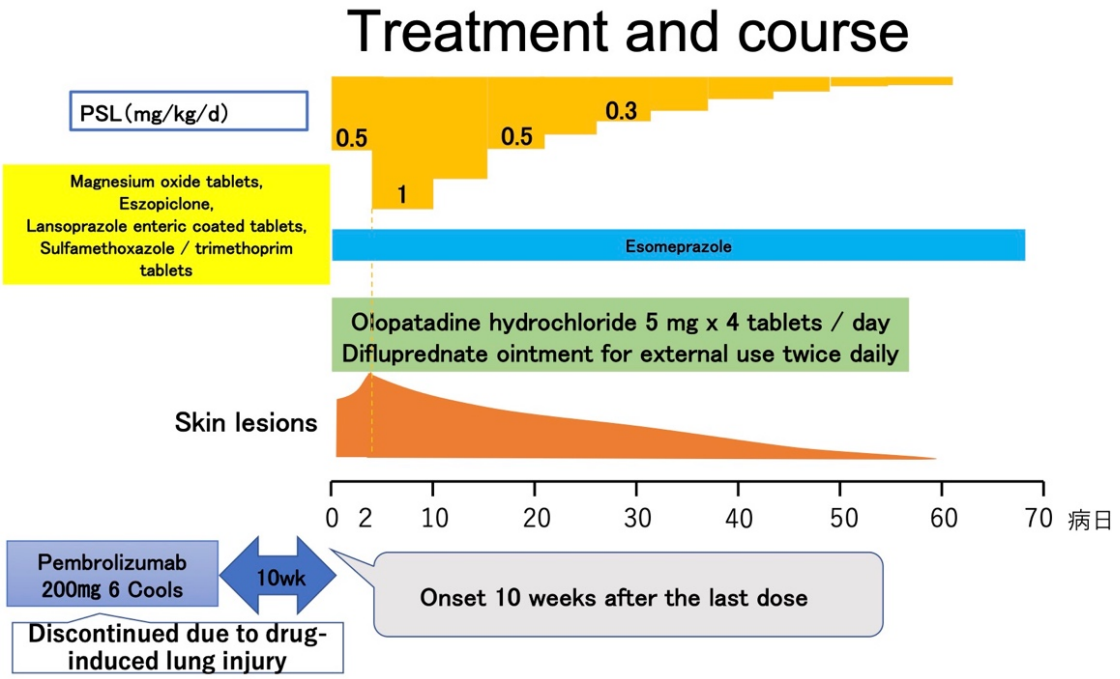

Figure 4. Treatment and course.

3. Discussion

The majority of toxicities caused by ICIs are low in severity, but some are more serious and require multidisciplinary management of side effects. To reduce the risk of experiencing severe toxicities, gathering information on different immune toxicities has been necessary and treatment practices have needed to adapt quickly[3, 5].

Side effects of irAE are different from conventional drugs[3, 4]. For examples, all organs can be injured and the passage or course of time is also various. There are many reports including skin disorders, digestive disorders (colitis, diarrhea), interstitial lung disease, myasthenia gravis, myocarditis, rhabdomyolysis, neuropathy, liver dysfunction, kidney disorder, encephalitis, endocrine disorders (Type I diabetes, thyroid dysfunction, adrenal insufficiency, hypophysitis) and so on. The incidence of skin disorders is 17-35%, such as mild form of erythematous papules, toxic epidermal necrolysis, Stevens-Johnson syndrome, psoriasis-like rash, lichen-like rash, autoimmune bullous disease, etc[6,7]. Recent report indicated that the most prevalent dermatological toxicities were alopecia (27%), pruritus, and rash (10%). Remarkably, the prevalent severity was graded 1−2 for both alopecia, pruritus and rash[6].

In the present case, a rash appeared 10 weeks after the end of anti-PD-1 antibody administration. In cases reported in Japan, the longest period from the end of anti-PD-1 antibody administration to the appearance of eruption was 8 weeks[8]. When examining patients during or after administration of ICIs, it is important to keep in mind that severe mucocutaneous disorders can occur regardless of the

duration of the last dose[9,10]. In addition, dermatological treatments and skin care must be tailored to the patient's condition[5,11].

Conflict of interest disclosure

None declared.

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