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CORRESPONDENCE

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Toxic epidermal necrolysis as a complication of pembrolizumab treatment in a lung cancer patient

Dear Editor,

Pembrolizumab is an anti-programmed death-1 (PD-1) checkpoint inhibitor. Pembrolizumab has been associated with numerous cutaneous adverse side effects, including Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), which are rare but potentially fatal.[1,2]

A 72-year-old Japanese female with stage IV lung cancer and multiple bone metastases received full doses of pembrolizumab, carboplatin, and pemetrexed as first-line treatment. In addition, she had taken celecoxib, lansoprazole, calcium carbonate, multivitamin, and fentanyl citrate as regular medications, which were continued for more than several months without any changes. She noticed pruritus and painful erythema on the trunk and limbs 14 days after the second administration of pembrolizumab, carboplatin, and pemetrexed sodium hydrate (Figure 1A). Six days later, the lesions progressed to palpable diffuse erythema involving 80% of the body surface area (BSA) with a positive Nikolsky's sign (30% of the BSA; Figure 1B). In addition, erosions developed on the lip mucosa and genitalia. She had slightly elevated

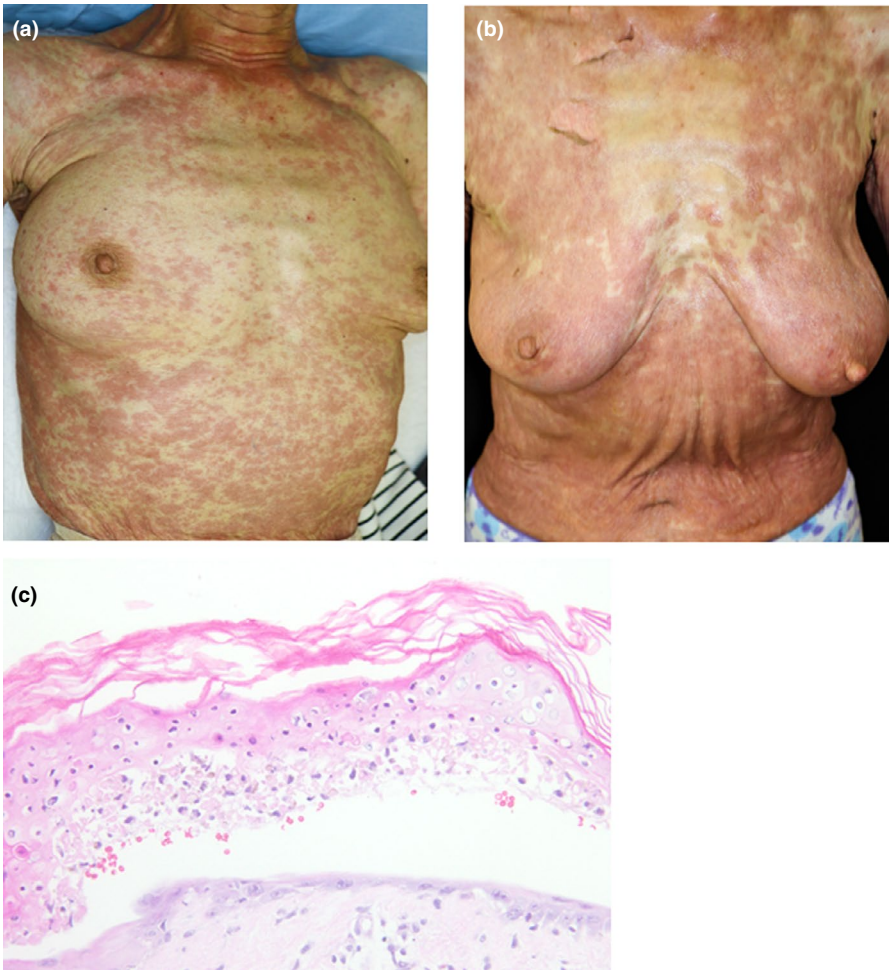

FIGURE 1 Clinical features and histopathologic features. (A) Clinical image of the patient at the initial visit showing confluent erythema of the trunk. (B) Expanded diffuse erythema and multiple erosions of the trunk. (C) Histopathologic findings showed full-thickness epidermal necrosis (HE × 400)

fever, but no serologic findings suggestive of active infection, such as cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and mycoplasma. A skin biopsy of the upper extremity indicated full-thickness epidermal necrosis (Figure 1C). She was diagnosed with TEN based on these findings. The severity of illness score for toxic epidermal necrolysis (SCORTEN) scale was 3. She discontinued all drugs and was administered 1000 mg of methylprednisolone pulse therapy and intravenous immunoglobulin (IVIG) at a total dose of 2 g/kg. Oral prednisolone (1.2 mg/kg daily) was initiated, and she gradually recovered, after which prednisolone was tapered over 4 weeks. When her symptoms had resolved, we performed a drug-induced lymphocyte stimulation test (DLST) for pembrolizumab, carboplatin, pemetrexed, and all other regular medications, including celecoxib; the DLST was only positive for pembrolizumab (stimulation index, 275%). Because immune checkpoint inhibitors, such as pembrolizumab, independently trigger an immune response, the DLST results could be a false-positive. Patch tests for concomitant drugs were needed to establish the cause of TEN; however, the patient declined.

Cutaneous adverse events while on anti-PD-1 therapy are common.[2] Moreover, skin rashes greater than grade 3 are rare, especially in lung cancer.[2] But, patients developing SJS/TEN related to anti-PD-1 therapy, including pembrolizumab, have recently been reported.[1,2] Carboplatin and pemetrexed were added to the anti-PD-1 treatment regimen for lung cancer in the current patient. Thus, pembrolizumab, carboplatin, pemetrexed, and celecoxib were considered to have induced TEN in our patient. We identified many reports of TEN induced by celecoxib,[3] but only a few cases induced by carboplatin or pemetrexed,[4] the DLSTs were negative. Celecoxib was regularly taken for more than several months without any side effects. We therefore thought that pembrolizumab was the most likely agent inducing TEN in our patient. A previous report suggested that anti-PD1 therapy increased the risk of a drug eruption alone or in combination with other drugs.[5] We suspected that pembrolizumab induced more severe cutaneous adverse events when combined with celecoxib and she developed TEN. Cutaneous adverse events in patients who are treated with anti-PD-1 checkpoint inhibitors, alone or in combination with other medications, should be closely observed.

DECLARATION SECTION

Approval of the research protocol: N/A.

Informed Consent: Informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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