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A Case of Guillain-Barré Syndrome and Stevens-Johnson Syndrome/Toxic Epidermal Necrosis Overlap After Pembrolizumab Treatment

Tomoyo Oguri, MD, PhD[1,2], Shinji Sasada, MD, PhD[1], Satoko Shimizu, MD[1], Risa Shigematsu, MD[1], Yumi Tsuchiya, MD[1], Kota Ishioka, MD[1], Saeko Takahashi, MD, PhD[1], Koichi Oki, MD, PhD[1], Yoshifumi Kimura, MD, PhD[1], Reishi Seki, MD[1], Shigemichi Hirose, MD, PhD[1], and Morio Nakamura, MD, PhD[1,3]

Abstract

A 76-year-old man was admitted to our hospital with Guillain-Barré syndrome (GBS), presenting with facial palsy, dysarthria, and dysphagia as Grade 3 immune-related adverse events (irAEs) due to pembrolizumab administration for Stage IV lung adenocarcinoma. Although prednisolone (1 mg/kg) was started for GBS due to the irAE, dark erythema and skin eruptions appeared on the patient's torso. Then erosion was observed on 18% of the body surface area and skin biopsy was performed. Finally, the patient was diagnosed with Stevens-Johnson syndrome/toxic epidermal necrosis overlap. Intravenous immunoglobulin therapy was started, and the skin symptoms improved, with the erosion becoming epithelial. He died of aspiration pneumonia related to GBS, although his neurological symptoms had improved after steroid and intravenous immunoglobulin therapy. This is the first reported case of pembrolizumab-induced GBS and Stevens–Johnson syndrome/toxic epidermal necrosis overlap. It is necessary to be careful that the possibility of other severe irAEs may occur simultaneously.

Keywords

Guillain-Barré syndrome, immune-related adverse event, pembrolizumab, Stevens-Johnson syndrome, toxic epidermal necrosis

Introduction

Pembrolizumab is an immune checkpoint inhibitor that blocks the programmed cell death-1 (PD-1) pathway in T-cells and is used in the treatment of metastatic lung cancer.[1] However, use of pembrolizumab leads to various immune-related adverse events (irAEs), which can be associated with severe decline in organ function and quality of life and fatal outcomes.[2] In this article, we report a case of severe irAE comprising Guillain-Barré syndrome (GBS) and Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN) overlap after pembrolizumab administration for lung adenocarcinoma.

Case Report

A 76-year-old man was diagnosed with left lower lobe lung adenocarcinoma, cT2bN2M1c (OSS, ADR) Stage IV with PD-L1 TPS90%. He received denosumab and radiation therapy (36 Gy, 12 fractions) on the left iliac bone because of severe pain, with pembrolizumab as second-line therapy. Two weeks later, he was admitted to our hospital because of severe joint and muscle pain in the extremities and exhibited a performance status of 3. A week later, bilateral facial palsy and bulbar palsy with associated dysarthria and dysphagia appeared. The patient also developed muscle weakness in the extremities with absent deep tendon reflexes. Brain magnetic resonance imaging

[1]Tokyo Saiseikai Central Hospital, Tokyo, Japan
[2]St Marianna University, Kawasaki, Kanagawa, Japan
[3]National Hospital Organization Kanagawa Hospital, Kawasaki, Kanagawa, Japan

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Corresponding Author:
Tomoyo Oguri, MD, PhD, Department of Clinical Oncology, St Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan.
Email: tomonet1206@gmail.com

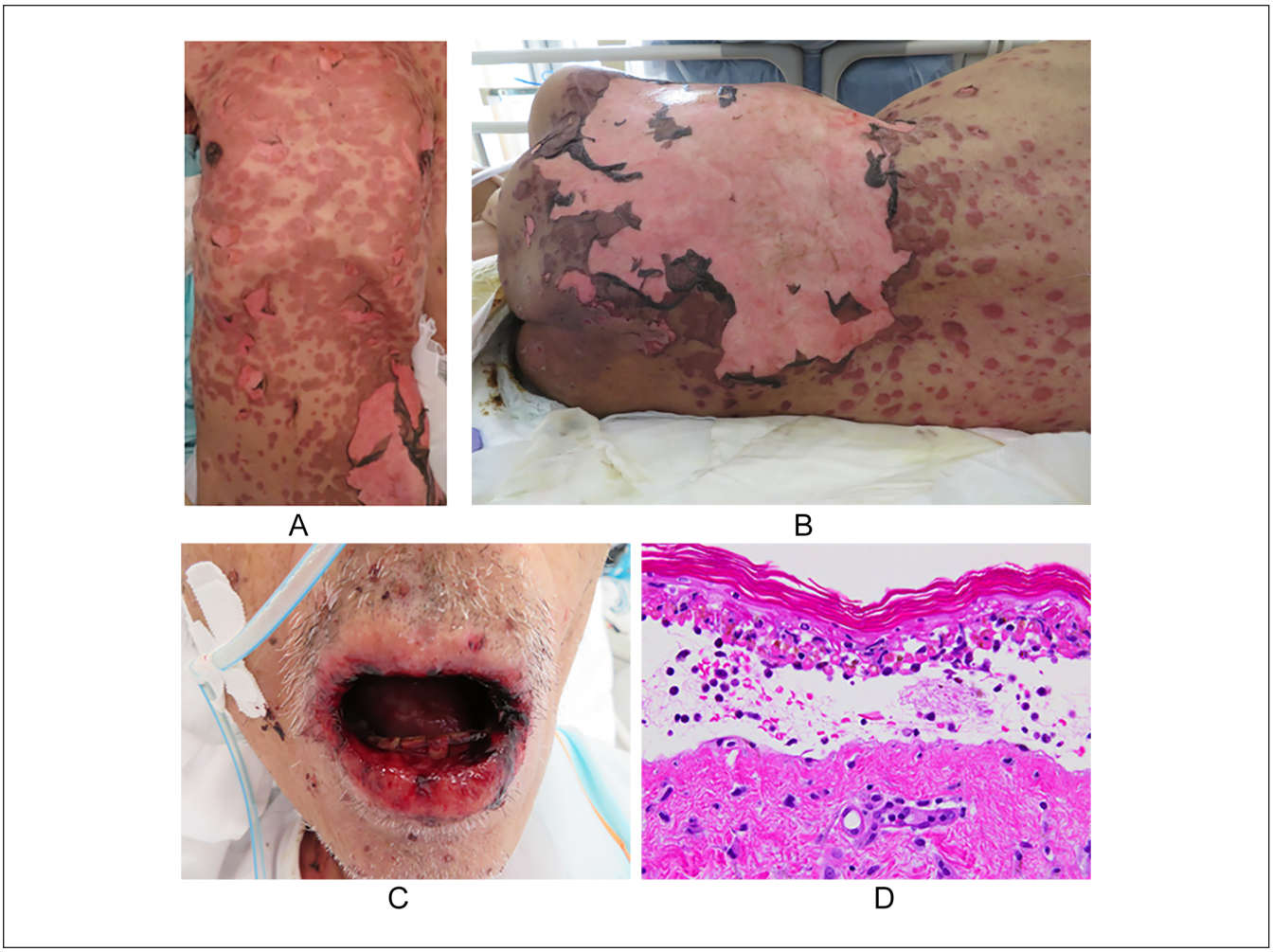

Figure 1. (A) Dark erythema and papules scattered across the patient's torso. (B) The Nikolsky phenomenon observed on the left lower back and abdomen. (C) Blood clots on the lips, and oral mucosal erosion. (D) Pathological examination using hematoxylin-eosin staining showing subepidermal blistering, extensive keratinocyte necrosis, and lymphocytic infiltration near the basal epidermal layer, and perivascular inflammatory cell infiltration with mild lymphocytes in the shallow dermis.

revealed no abnormalities. Meanwhile, nerve conduction studies revealed motor and sensory neuropathy in the upper and lower limbs. Cerebrospinal fluid (CSF) analysis revealed marked elevation of protein levels and pleocytosis with class II cytology indicating inflammatory cells with no evidence of metastatic cells.

CSF culture was negative, and serum mycoplasma pneumoniae antibody titer (CF method) was negative (less than 4 times). He was diagnosed with GBS based on the clinical manifestations and the results of the nerve conduction studies despite the negative results of anti-GM1 and anti-GQ1b ganglioside antibodies and pleocytosis in CSF analysis, which is an atypical finding in GBS. His GBS was assessed as Grade 3 irAE according to the Common Terminology Criteria for Adverse Events version 4.0. Although prednisolone (1 mg/kg) and acyclovir were administered, under suspicion for irAE and herpes zoster, respectively, which we had started for GBS on day 5 of hospitalization, the patient developed dark erythema and scattered papules on his torso (Figure 1A) on day 9. Subsequently, blisters and erosions appeared on 18% of his body surface area with Nikolsky phenomenon (Figure1B), blood clots on the lips, and oral mucosal erosion (Figure 1C). We then performed a skin biopsy. Pathological examination via hematoxylin-eosin staining revealed subepidermal blistering, extensive keratinocyte necrosis, and lymphocytic infiltration near the basal layer of the epidermis, and perivascular inflammatory cell infiltration with mild lymphocytes in the shallow dermis (Figure 1D); and the patient was diagnosed with SJS/TEN overlap. Intravenous immunoglobulin therapy (IVIG therapy, 400 mg/kg/d) was administered from day 9 for 5 days, and almost all skin erosions were epithelialized by day 42. Although his facial and bulbar palsy improved, the muscle weakness persisted. His respiratory condition rapidly deteriorated due to aspiration pneumonia, and he died on day 53.

Discussion

To the best of our knowledge, this is the first case report of pembrolizumab-induced severe GBS and SJS/TEN overlap.

The adverse effects of pembrolizumab, as well as other immune checkpoint inhibitors, can affect multiple organs. Therefore, any changes should be suspected to be treatment-related. According to CTCAE, irAEs are graded according to their severity. Moderate (Grade 2) to severe (Grades 3-4) irAEs may be associated with severe declines in organ function and quality of life, as well as fatal outcomes; hence, these toxicities require early detection and proper management.[2]

The incidence rate of irAEs in the nervous system is 0.1% to 12% and grade 3 to 4 severe neuromuscular disease are considered to be less than 1%, and 80% of these irAEs occur within 4 months after pembrolizumab administration,[1] like our case.

GBS is an acute demyelinating polyneuropathy with rapidly progressive, symmetric, and ascending weaknesses of the upper and lower extremities, with loss of deep tendon reflexes and variable sensory deficit. Similar to our patient, severe cases of respiratory failure by respiratory muscle weakness have been reported due to GBS as an irAE.[3,4] The following hypotheses have been suggested as possible mechanisms of irAE-induced GBS: loss of peripheral tolerance, T-regulatory cell deficit, and molecular mimicry between malignant melanocytes and other neural crest derivatives (eg, Schwann cells).[5,6] The recommended therapy for this condition is to permanently discontinue pembrolizumab and initiate intravenous prednisolone (1-2 mg/kg), tapering when toxicity resolves. IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases.[1] Although antiganglioside antibodies were negative in our case, PD-1 inhibitor-related AIDP was reportedly positive for GM2 and GalNAc-GD1a antibodies.[7]

Although skin toxicity is one of the most frequent irAEs, itching, erythema, papules, and vitiligo are common; however, reports of grade 3 to 4 events, such as SJS and TEN, are rare.[8] TEN is more frequently associated with anti-PD-1 therapy than with other anticancer drugs[9,10] and permanent discontinuation of immunotherapy, in the setting of severe or life-threatening bullous disease (grade3-4) as irAE, including all cases of SJS and TEN.[2] Reportedly, skin toxicity occurs early in the treatment course (within the first few weeks after initiation).[11]

SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving $<$10%, 10% to 30%, and $>$30% body surface area, respectively.[12] SJS/TEN is a serious and life-threatening disease caused mainly by drugs, characterized by fever and severe mucosal eruptions of the eye mucosa, lips, and vulva, and erythema, blisters, and erosions based on necrotizing epidermal disorders. Pathological findings include edema in the upper dermis and perivascular cell infiltration. Eosinophils may exhibit necrotic changes in the epidermis progress, resulting in necrosis of all epidermal layers and subepidermal blistering.[13]

TEN are often caused by pharmaceuticals; however, they can also be caused by infectious diseases such as viral or systemic disease.[2] In our case, wound cultures and mycoplasma antibodies were negative, and no findings indicated infection.

Although the drug-induced lymphocyte stimulation test (DLST) is a useful test in the search for causative agents in severe drug eruptions, it may contain false positives depending on the target drug; therefore, using patch tests or other tests in combination is desirable to determine the causative agent. In particular, nonsteroidal anti-inflammatory drugs and acetaminophen are associated with increased lymphocyte proliferation due to inhibition of prostaglandin E2 synthesis, which may result in a positive test result of DLST. In this case, the DLST of acetaminophen was also positive; however, no relapse occurred with re-administration, and it was safe to use before pembrolizumab administration. Thus, we suspected a false-positive result.

We encountered a rare case of pembrolizumab-induced irAE complicated with GBS and SJS/TEN overlap. Despite the early steroid administration for GBS, SJS/TEN overlap occurred. The patient died of GBS-associated aspiration pneumonia, although his symptoms had improved after steroid and IVIG therapy. Careful consideration of the possibility that other severe irAEs may simultaneously occur is necessary.

Conclusion

This is the first reported case of pembrolizumab-induced GBS and SJS/TEN overlap. It is necessary to be weary of the possibility that other severe irAEs may occur simultaneously.

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Author Contributions

Tomoyo Oguri: Conceptualization and writing-original draft. Shinji Sasada: Writing-review and editing. Satoko Shimizu: Data curation. Risa Shigematsu: Data curation. Yuumi Tsuchiya: Data curation. Kota Ishioka: Data curation. Saeko Takahashi: Data curation. Koichi Oki: Writing-review and editing. Yoshifumi Kimura: Writing-review and editing. Reishi Seki: Writing-review and editing. Shigemichi Hirose: Writing-review and editing. Morio Nakamura: Writing-review and editing.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Tomoyo Oguri is an employee of Astra Zeneca K.K.

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Ethics Statement

Ethical approval to report this case was obtained from the Saiseikai Central Hospital institutional Review Board (CR-115).

Informed Consent

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

ORCID iD

Tomoyo Oguri https://orcid.org/0000-0002-7655-1517

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