中文題目：在牙齦鱗狀細胞癌患者身上由吉舒達引起的史蒂芬強生症候群和毒性表皮壞死症候群

英文題目：A case of pembrolizumab-related Stevens-Johnson syndrome and toxic epidermal necrolysis-like reactions in a patient with gingival squamous cell carcinoma

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Introduction

Immune checkpoint inhibitors (ICI) are an emerging class of drug for advanced malignancies. They are monoclonal antibodies targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or the programmed cell death protein 1 (PD-1) or its ligand programmed death-ligand 1(PD-L1). CTLA-4 and PD-1 signaling serve to attenuate T-cell activation and effector function, for maintaining peripheral tolerance in normal physiology. The tumor environment takes advantage of these signaling pathways to avoid elimination by the immune system. Thus, blockage of those mechanisms by ICI enhances the intrinsic ability of the immune system to destroy tumor cells. However, inflammatory side effects occur due to the interference between ICI and peripheral immune homeostasis, which termed immune-related adverse events (iRAEs), affecting organ systems, including cutaneous reactions with pruritic sensation and different morphologies of rashes, sometimes even life-threatening with similarities to Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Case report

We present a 79-year-old Taiwanese male with hypertension and type 2 diabetes mellitus. He was previously a heavy smoker with 1 pack cigarette per day for about 30 years, he denied usage of betel nuts and alcohol drinking. His family history was unimpressive. He initially presented with a painless rubbery mass in left submandibular area, followed by toothache for one month. Otorhinolaryngology out-patient department visit on 2021/06/07 revealed a 2.5 cm ulcerative, exophytic tumor over left lower gingiva and a fixed non-tender mass over level Ib and II of left neck. Biopsy of the mass revealed a final diagnosis of left lower gingival squamous cell carcinoma, moderately differentiated. PD-L1 22C3 immunohistochemistry assay (Agilent/Dako) was completed and his Tumor Proportion Score (TPS) was 18% and his Combined Positive Score (CPS) was 35. Complete workup revealed no intrathoracic metastasis on chest CT and no lesion in brain parenchyma on brain MRI

image, clinical stage was T4N2bM0. The first course of cancer-related immunotherapy for him was initiated with pembrolizumab 100 mg on 28th June, 2021, and the second course on July 19th. Itchy and redness skin rash over four extremities and body trunk developed a week after the second course of pembrolizumab, he visited our out-patient department on July 29th, some oral and topical steroids were prescribed. However, his symptoms progressed in the following days with lips, oral and scrotal swelling and ulcerative wounds. Difficulty in mouth opening due to pain, which lead to decreased in oral intake also mentioned. He was then brought to our emergent department and admission to ward on August 1st. Generalized pruritic erythema with central dusky red was observed. The lesions were not painful and mild infiltrative. No ulcers and erosions found on the skin but over oral and genital area. We consulted Dermatologist, skin biopsy over abdominal area was done and showed skin tissue with epidermal necrosis, apoptotic keratinocytes and subepidermal separation. Perivascular lymphohistiocytes and eosinophils infiltration in the dermis. Pathology report was compatible with SJS. We also consulted Plastic surgeon as multiple ruptured bullae occurred since August 10th. Total body surface area (TBSA) of skin damage was 13% (right arm 1%, left arm 1%, right leg 3%, left leg 3%, facial area 2%, trunk 3%) on August 10th, and progressed to 49% (right arm 1%, left arm 2%, right leg 15%, left leg 15%, facial area 2%, anterior trunk 7%, posterior trunk 7%) on August 12th, TEN was impressed and he was escorted to burn unit for intensive wound care. We kept intravenous steroids, empirical antibiotics, high caloric nutrition and fluid support. Wound care with non-adhesive dressings for the ruptured bullae area and compression with elastic bandages also applied. After treatment, his skin rash gradually darkens, and no new lesion was observed, TBSA improved to 9% (bilateral arms, abdominal and perineal area 3%, right leg 3%, left leg 3%) on August 16th. He was transferred to ordinary ward on August 19th under 4% of TBSA (bilateral arms, abdominal and perineal area 2%, right leg 1%, left leg 1%) We tapered steroids step by step from intravenous to oral, and gradually took off on 23rd August, 2021. He was then transferred back to ordinary ward and discharged under stable condition afterward.

Discussion

Although the exact mechanisms explaining patients develop SJS/TEN by ICI are unclear, PD-1/PD-L1 axis was suspected to play a role in maintaining epidermal integrity in some study. One of the studies reported that human skin samples from

patients who developed cutaneous reactions to a PD-1 inhibitor, provided resembled gene expression profile to that from patients with SJS/TEN, regardless or the severity of skin lesion, which also indicated that ICI induced changes in injured skin transcriptome similar to those in SJS/TEN patient. Another study performed that increased surface PD-L1 expression on human keratinocytes isolated from oral cavity was inducible by interferon-c, suggesting that increased PD-L1 expression in an inflammatory environment may serve as a protective mechanism for keratinocytes. Moreover, blockade of the PD-1/PD-L1 pathway could allow autoreactive CD8+ T cells targeting keratinocytes displaying self-antigens to become activated and proliferate. In literature review, SJS/TEN-like reactions occurred in a median duration of 3 weeks in pembrolizumab, and about 4 weeks in the case we reported. Development of iRAEs by a ICI has been correlated with favorable cancer response. However, none of the studies in literature review described drug rechallenge in cases with SJS/TEN, a mortality rate of 60% also reported.

Conclusion

SJS/TEN syndrome and other severe cutaneous iRAEs were relatively rare, and current evidence did not identify certain risk factors, but the importance of PD-1/PD-L1 signaling to the maintenance of immune tolerance in mucocutaneous diseases has been highlighted. Nevertheless, genetic differences in genes controlling immune regulation also served as one possible explanation to the mechanism. Further clinical, pathological, and basic science studies should be conducted for more information on the mechanisms, characteristics, and optimal management.