BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Steven-Johnson Syndrome/Toxic Epidermal Necrolysis is Associated with PD-1/PD-L1 Inhibitors Usage: A Case Series

Riqu Cao[1], Tianhong Xu[1,*]

[1]Department of Dermatology, Hangzhou Third People's Hospital, Hangzhou, Zhejiang, China
*Correspondence: tianhongxu2024@163.com (Tianhong Xu)

Abstract

Aims/Background The increasing adoption of inhibitors of programmed cell death-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), in the treatment of multiple cancer types in China has started to garner broader attention due to the occurrence of immune-related adverse events (irAEs), especially life-threatening skin reactions such as Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Isolated case reports have described SJS/TEN associated with PD-1/PD-L1 inhibitors usage. In this paper, we presented a series of cases of SJS/TEN following the use of PD-1/PD-L1 inhibitors in a dermatology hospital located in Zhejiang Province of China in the past several years, summarizing characteristics of these cases and providing a reference of management.

Methods We retrospectively reviewed all the medical records of inpatients diagnosed with SJS/TEN in the Hangzhou Third People's Hospital from 2012 to 2024. We analyzed and compared the situation of SJS/TEN onset, types of PD-1/PD-L1 inhibitors used, score of severity, laboratory findings, and essential therapies of the patients who had received PD-1/PD-L1.

Results We identified 12 SJS/TEN patients who had been treated with PD1/PD-L1 inhibitors: sintilimab had been used in six patients; tislelizumab in two cases; toripalimab, keytruda and cadonilimab each in one case; and an unknown prescription in one case. The longest duration between the first PD-1/PD-L1 inhibitor dose and the SJS/TEN diagnosis recorded was nine months whereas the shortest was 11 days. Half of the selected patients received chemotherapy at the same time. More than two types of therapies were applied to the cases, except for two cases with mild SJS.

Conclusion This study unveils a potential, under-recognized cause of SJS/TEN in the cancer patients after analyzing the cases of SJS/TEN in cancer patients with prior exposure to PD-1/PD-L1 inhibitors. This paper also provides clue about the prominent features of SJS/TEN aforesaid, offering insights on the effective management measures for optimizing clinical safety.

Key words: Steven-Johnson syndrome; toxic epidermal necrolysis; programmed cell death-1; programmed death-ligand 1; case series

Submitted: 31 July 2024 Revised: 25 August 2024 Accepted: 12 September 2024

How to cite this article:
Cao R, Xu T. Steven-Johnson Syndrome/Toxic Epidermal Necrolysis is Associated with PD-1/PD-L1 Inhibitors Usage: A Case Series. Br J Hosp Med. 2024.
https://doi.org/10.12968/hmed.2024.0477

Introduction

Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a type of rare but severe drug eruption, with a usually association with the usage of allopurinol, lamotrigine, sulfasalazine and carbamazepine (Roujeau et al, 1995). Its relation with other new drug agents like immune checkpoint inhibitors (ICIs) remains largely unclear. Inhibitors of programmed cell death-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), are effective ICIs that block the activity of

inhibitory immune checkpoint proteins and promote T cell activation to achieve anti-tumor immune effects (Kruger et al, 2019). The rate of cutaneous immune-related adverse events (irAEs) is rising in tandem with the rising use of ICIs in various tumor types. It has been reported that cutaneous adverse events occurred in 34–42% of PD-1 inhibitor monotherapy patients and about 20% of PD-L1 inhibitor monotherapy patients (Collins et al, 2017; Sibaud, 2017). Besides that, more common complications including morbilliform or lichenoid eruptions, vitiligo, pruritus, bullous disorders, and psoriasiform or eczematous dermatitis (Johnson et al, 2018; Postow et al, 2018; Sibaud, 2017), as well as severer complication like SJS/TEN, have also been reported.

Recent research has revealed a rise in the anecdotal cases of PD-1/PD-L1 inhibitors-associated SJS/TEN (Li et al, 2022; Yang et al, 2022). In this study, we gathered the clinical data of the SJS/TEN inpatients who had used PD-1/PD-L1 inhibitors in the last 12 years from January 2012 to January 2024 in Hangzhou Third People's Hospital. Data on the latency, course of illness, laboratory findings, treatments and outcomes of these patients were also acquired and described, for creating a more complete picture regarding the characteristics of SJS/TEN associated with PD-1/PD-L1 inhibitors usage.

Methods

Patient Data

We retrieved clinical data of the inpatients diagnosed with SJS/TEN in Hangzhou Third People's Hospital from January 2012 to January 2024 and picked out the cases of PD-1/PD-L1 inhibitors usage prior to the incidence of disease. In the present study, only the patients who had used PD-1/PD-L1 inhibitors prior to the onset and diagnosis of the disease were included. However, patients diagnosed with SJS/TEN who had used known SJS/TEN-related drugs including allopurinol, lamotrigine, sulfasalazine and carbamazepine were excluded.

The SJS/TEN was diagnosed by the physicians according to a set of typical feature such as widespread blister formation on erythematous skin and lesions on mucous membranes, coupled with histopathologic findings of apoptotic keratinocytes, widespread epidermal necrosis, and infiltration by lymphocytes, histiocytes and eosinophils, with the latter occurring at a minimal extent (Lerch et al, 2017). The SJS/TEN is stratified into three classifications based on the area of affected skin in view of the total body surface area (Bastuji-Garin et al, 1993):

(1) SJS is defined by a skin involvement of $<10\%$;

(2) SJS/TEN is defined by a skin involvement of 10–30%;

(3) TEN is defined by a skin involvement of $>30\%$.

The affected skin generally suffer from blisters formation, partial or complete detachment, and dislodgment of intact superficial epidermis (Nikolsky's sign).

We used the Adverse Drug Reaction (ADR) Probability Scale (Naranjo Scale) to assess the causality between exposure to PD-1/PD-L1 inhibitors and the development of SJS/TEN (Naranjo et al, 1981). The causal relationship between PD-1/PD-

L1 inhibitors and SJS/TEN is viewed as definitive in the event that the score was 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.

To predict mortality of SJS/TEN, Bastuji-Garin et al (2000), developed a severity-of-illness score for toxic epidermal necrolysis (SCORTEN) based on seven independent risk factors for epidermal necrolysis, including age >40 years, malignancy, tachycardia, initial skin detachment >10%, serum urea >10 mmol/L, serum glucose >14 mmol/L, and serum bicarbonate <20 mmol/L, with each factor fulfillment scoring one point. The total score of this method is 7, and the corresponding forecast mortality rates are as follows: 1%, 4%, 12%, 32%, 62%, 85%, 95% and 99%, respectively (Bastuji-Garin et al, 2000).

Demographic, clinical and laboratory data, as well as results from skin biopsy (when available), were retrieved for each case. The clinical course of the selected patients, including hospitalization time and specific therapies were assessed. All the measures were defined as the first measurement performed in clinic.

The present work is reported in line with the SCARE criteria (Sohrabi et al, 2023). This study is in compliance with the Declaration of Helsinki and was approved by the institutional research ethics committee of Hangzhou Third People's Hospital (approval file number: 2024KA106). Since all the diagnosis and treatment data used were obtained from the archive, the procedure for obtaining patients' informed consent has been exempted by the ethics committee as long as patients' privacy and data confidentiality were guaranteed.

Statistical Analysis

Descriptive statistics analysis were calculated for all study variables. Quantitative variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate, and categorical variables are presented as frequencies and percentages.

Results

There were twelve SJS/TEN cases that were treated with PD-1/PD-L1 inhibitors before between January 2012 and January 2024 identified. According to the results of Adverse Drug Reaction (ADR) Probability scale, all the twelve cases indicate that the occurrence of SJS/TEN and the PD-1/PD-L1 inhibitors usage are probably related.

Demographic and Clinical Characteristics

The baseline demographic and relevant information for all the cases are presented in Table 1. The majority of patients were male (9 cases, 75.0%), and their average age was 63.4 years (median age: 64.5 years, and a range of 50 to 74 years). The most common type of cancer in this sample was lung carcinoma, occurring in 4 cases (33.33%), followed by gastric cancer (3 cases, 25%) and lymphoma (2 cases, 16.7%). Prostate cancer, esophagus cancer, and cervical and endometrial cancer respectively occurred in the remaining three cases. Four of the cases had hyper-

Table 1. Clinical characteristics and PD-1/PD-L1 usage among the twelve patients.

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	50	64	51	73	74	58	68	65	67	63	56	72
Sex	Female	Male	Male	Male	Male	Male	Male	Male	Female	Male	Female	Male
Comorbidities	CA, erythema, dental ulcer	Hypertension, CA, diabetes, pneumonia	CA	Hypertension, CA	CA, urticaria	Chronic hepatitis B, CA, erythema	CA	Hypertension, CA	CA	CA	Hypertension, CA	CA
Tumor	Diffuse large B cell lymphoma, DL-BCL, breast	Perineum NK/T cell lymphoma, pancreas, central nervous and bone marrow metastases	Gastric malignant tumor	Prostatic cancer, secondary lymphoid malignancies	Squamous cell lung carcinoma	Esophagus cancer, lung and renal metastasis	Lung squamous carcinoma with bone metastasis	Lung cancer, secondary malignancy of the liver, bone, and lymph nodes	Gastric carcinoma	Pulmonary malignant tumor	Cervical and endometrial cancer, multiple metastatic carcinomas	Gastric tubular adenocarcinoma, hepatic metastases
Chemotherapeutic drugs at the same time	No	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes
PD-1/PD-L1 inhibitors	Unknown	Sintilimab	Toripalimab	Tislelizumab	Tislelizumab	Sintilimab	Sintilimab	Sintilimab	Sintilimab	Keytruda	Cadonilimab	Sintilimab
Duration between the first use of PD-1/PD-L1 inhibitors and SJS/TEN diagnosis	9 months	19 days	66 days	Unknown	Unknown	8 months	54 days	14 days	1 month	Half month	11 days	1 month
Time from onset to confirmed diagnosis	13 days	11 days	7 days	7 days	10 days	15 days	10 days	3 days	8 days	6 days	3 days	8 days
Skin involvement	TEN	TEN	SJS	TEN	TEN	TEN	SJS	TEN	TEN	SJS	SJS	TEN
SCORTEN score	/	4	/	4	/	3	3	3	/	/	/	/
Survived to discharge from hospital	Yes	Yes	Yes	Self-discharge	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Length of stay	13 days	19 days	4 days	5 days	4 days	45 days	14 days	20 days	15 days	8 days	10 days	22 days
Therapies	Methylprednisolone + gamma globulin	Methylprednisolone + gamma globulin + ofloxacin + human albumin	Methylprednisolone	Methylprednisolone + hemoperfusion	Methylprednisolone + gamma globulin	Methylprednisolone + gamma globulin + sulperazone + hemoperfusion + human albumin + moxifoxacin + meropenem	Methylprednisolone + gamma globulin + human albumin	Methylprednisolone + gamma globulin + ofloxacin + linezolid + human albumin	Methylprednisolone + gamma globulin + human albumin	Methylprednisolone	Methylprednisolone + gamma globulin	Methylprednisolone + gamma globulin + human albumin + hemoperfusion + ceftriaxone + rhG-CSF + Recombinant human thrombopoietin Injection

Abbreviations: CA, cancer; DL-BCL, diffuse large B-cell lymphoma; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; rhG-CSF, recombinant human granulocyte colony-stimulating factor; SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.

Table 2. Heart rate and other laboratory data of the patients (n = 12).

Parameters	Characteristics (mean ± SD or median (IQR))
Heart rate (bpm)	88 ± 11
Blood glucose (mmol/L)	7.20 (4.99, 10.40)
Urea (mmol/L)	7.60 ± 3.25
Creatinine (μmol/L)	71 ± 21
Neutrophils (10^9/L)	3.30 (2.09, 6.39)
Lymphocyte (10^8/L)	5.85 (4.30, 9.00)
Alanine transaminase (U/L)	21.5 (15.5, 40)
Aspartate aminotransferase (U/L)	27.5 (20, 32.5)

SD, standard deviation; IQR, interquartile range.

tension, and one of them also had diabetes mellitus. Three cases reported an early manifestation of skin allergy like erythema and urticaria following the use of PD-1/PD-L1 inhibitors. In Patient 1, after the second course of PD-1/PD-L1 inhibitor, curable red spots started to appear on the body; until 13 days before the diagnosis of TEN, levofloxacin and amoxicillin tablets were taken by this patient for oral ulcers. Patient 2 received antibiotic 11 days before admission due to a pulmonary infection. A combination of chemotherapeutic drugs and PD-1/PD-L1 inhibitors were used by 6 cases.

The most common type of PD-1/PD-L1 inhibitor associated with SJS/TEN found in this study was sintilimab (6 cases, 50%); it was reported by two patients using tislelizumab, three patients using toripalimab, keytruda, and cadonilimab, respectively, and one patient with unknown prescription.

In our study, the latency from the first usage of PD-1/PD-L1 inhibitors to the occurrence of SJS/TEN varied from 11 days to 9 months. For instance, Patient 6 received the sintilimab injection therapy since August 2020 but he did not present with any relevant symptoms of the disease until April 2021.

The SCORTEN score for the cases with complete data ranged from 3 to 4 points, indicating a forecast mortality rate of 32% and 64%, respectively.

Clinical Course and Outcomes

Intravenous treatment was administered with methylprednisolone in all cases, and all TEN patients had undergone through multiple main therapies, including infusion of immunoglobulin and hemoperfusion, and hormone therapy. The average length of stay for these patients was 14.9 days, ranging from 4 to 45 days. Six patients received human albumin as a nutritional supplement. Among all the included patients, only Patient 4 lost to be followed up on after self-discharge, and the remaining cases showed improvement and were discharged.

Laboratory Index and Pathology

Table 2 tabulates data of heart rate—an independent risk factor—and other important laboratory indexes. The average heart rate was 88 ± 11 bpm, the mean urea level during admission was 7.60 ± 3.25 mmol/L, and the creatinine level was 71 ± 21 μmol/L. The data of serum glucose and liver function index are expressed as medians and quartiles since they do not comply with the normal distribution. All

the patients were classified as having normal liver function with a median alanine transaminase level of 21.5 U/L (15.5, 40) and a median aspartate aminotransferase 27.5 U/L (20, 32.5). The blood glucose on admission underwent a huge fluctuation (7.20 mmol/L [4.99, 10.40]). The patients also generally manifested low lymphocyte count, with a median number of 5.85 (4.30, 9.00) $\times 10^8$/L at admission, but presented with leukocytosis marked by a median leukocyte count of 3.30 (2.09, 6.39) $\times 10^9$/L. In Patients 11 and 12, skin biopsies were performed and the histopathological findings showed subepidermal blisters with widespread necrosis and apoptotic keratinocytes associated with lymphocytic inflammatory infiltrate (Figs. 1,2).

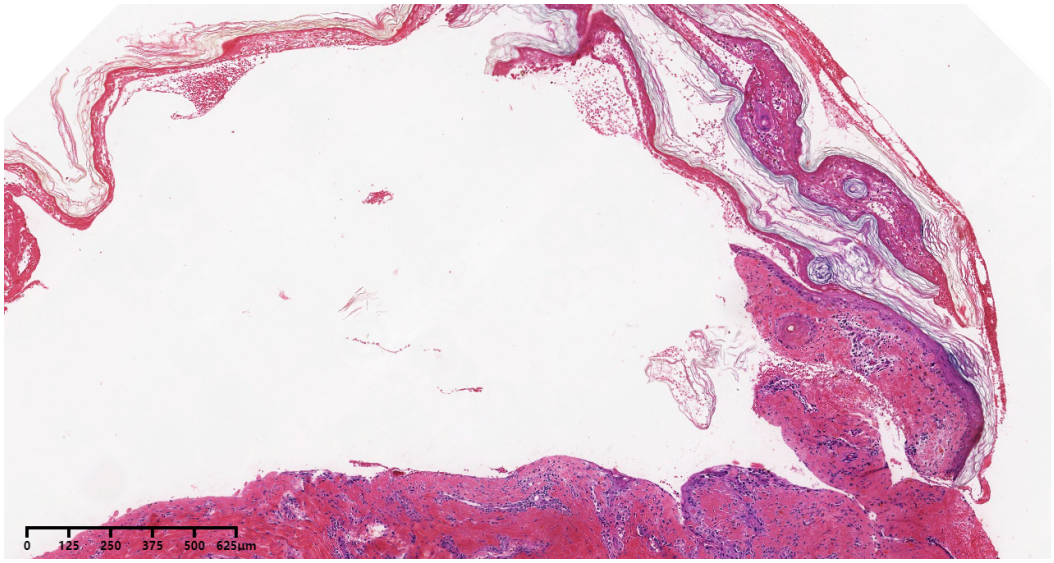

Fig. 1. Pathologic features associated with Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) following PD-1/PD-L1 inhibitors usage, showing widespread necrosis, apoptotic keratinocytes, and lymphocyte infiltration (Patient 11). PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

Discussion

The PD-1 is a transmembrane protein with 288 amino acids that is expressed in a variety of immune cells. It mainly consists of extracellular IgV-like domain region, the hydrophobic transmembrane region, and cytoplasmic region. (Chen et al, 2022). In normal physiological conditions, the main function of the PD-1/PD-L1 pathway is to maintain immune homeostasis. However, PD-L1 expressed by cancer cells binds to PD-1 on the surface of T cells, thereby inhibiting T cell activation and leading to cancer immune escape (Cheng et al, 2020; Yi et al, 2022; Zhao et al, 2022; Zou et al, 2023). PD-1/PD-L1 inhibitors can hamper their binding, restoring T cells activity to enhance anti-tumor immunity (Arranz-Nicolás et al, 2021; Jiang et al, 2019). Since 2019, a growing number of antagonistic antibodies against PD-1 have been approved in China for treating different types of cancer; however, this form of therapy elicits an antitumor T cell response and enhances immunological activation leading to immune-related adverse. This provides a probable rationale

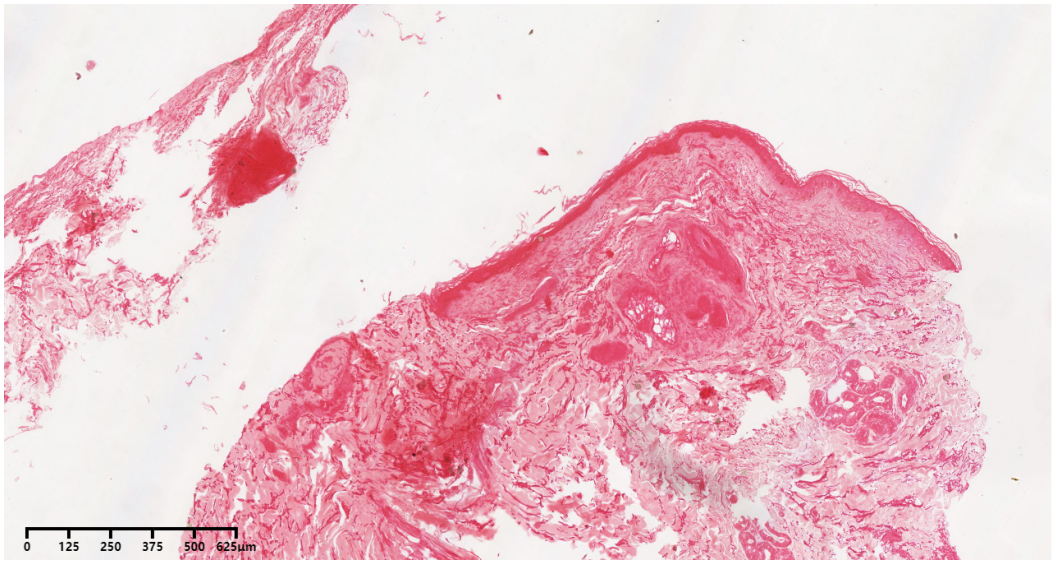

Fig. 2. Epidermal necrosis and normal epidermis on the right side of the image (Patient 12).

for why 12 cases of SJS/TEN in our hospital occurred between the latest several years 2020–2023.

Almost all the ICIs can trigger cutaneous irAEs, including rash of any grade or rare high-grade skin adverse events. Until now, a few reports have described PD-1/PD-L1 inhibitors-associated SJS/TEN, like cases related to sintilimab and cadonilimab (Chen et al, 2023; Li et al, 2022, 2023). The occurrence of irAEs is probably related to the disruption of the balance between PD-1 and PD-L1. When the PD-1 pathway is pharmacologically blocked, T cell responses are promoted, leading to the proliferation of self-reactive T cells with resultant autoimmunity (Yoest, 2017), while PD-L1 expression by epidermal keratinocytes is increased (Vivar et al, 2017), activating CD8+ cytotoxic T cell to target and decimate keratinocytes (Goldinger et al, 2016; Ziemer et al, 2021). This mechanism accounts for the progression of SJS/TEN. Another potential mechanism involves cross-reactivity between antigens, for instance, T cells recognizing tumor antigens may also be reactive against skin epitopes (Berner et al, 2019; Hua et al, 2016).

Based on our findings, the onset of SJS/TEN may take an incubation period of days to months since the first use of anti-PD-1/PD-L1 therapies, and in several cases, light skin allergic reactions had occurred at the early stage of the treatment, presaging the SJS/TEN eruption, since ICIs-induced SJS/TEN-like reaction has been reported to develop after a slow progression of lichenoid or morbilliform (Vivar et al, 2017). As reported, concomitant chemotherapy use or infection may induce SJS/TEN since they were significant independent predictive risk factors for irAEs (Huang et al, 2021). This is evident in the current study, as we observed that a patient who injected with only sintilimab did not suffer an SJS/TEN episode until a chemotherapeutic drug was administered. Since cutaneous adverse reactions like urticaria, maculopapular rash and pruritus are commonplace among the PD-1/PD-L1 inhibitors users, we postulate that patients with prior skin reactions are more likely to develop SJS/TEN when other therapies are combined in the treat-

ment regimens or when an infection occurs, a phenomenon that warrants clinicians' vigilance.

SCORTEN is a specific severity-of-illness score for SJS/TEN, that predicts mortality with high accuracy (Cartotto et al, 2008; Hu et al, 2012). In this study, the SJS/TEN cases had a SCORTEN score of 3 or 4 points based on available data, and all of the cases survived till hospital discharge, except 1 case was lost to follow up.

Another interesting observation was the lymphocyte count reduction. Furthermore, as in most of our patients, neutrophile granulocyte count was mildly elevated, but there is no scientific rationale to explain this pathological finding.

To manage PD1/PD-L1 inhibitors-associated SJS/TNE, the first step is to discontinue ICIs treatment and initiate immunosuppressive treatment promptly. It has been found that simple strategy is not potent enough to control the progression of the disease due to the resistance developed against corticosteroids and intravenous immunoglobulin (Zhang and Wu, 2023). In our cases, more than two specific types of treatments are essential for TEN cases, apart from the supportive care. In recent years, Tumor necrosis factor-α (TNF-α) inhibitors like adalimumab have been recommended as a viable alternative for shortening the clinical course, given that SJS/TEN is associated with a high level of TNF-α (Chen et al, 2023).

Conclusion

The current study emphasizes the correlation of PD-1/PD-L1 inhibitors with SJS/TEN development, which requires more in-depth studies for validation. In this paper, we provide some characteristic clues to SJS/TEN that are associated with the use of PD-1/PD-L1 inhibitors, such as latency period, potential signs like early mild rash, potential threats from combined chemotherapy and antibiotics, the degree of severity and clinical outcomes, *etc*., which could point to severe cutaneous adverse caused by PD-1/PD-L1 inhibitors.

Key Points

- This study gathered the data of patients who had previously used PD-1/PD-L1 inhibitors but later were diagnosed with SJS/TEN in a dermatology hospital.
- This study highlights the correlation between SJS/TEN development and PD-1/PD-L1 inhibitors utilization, offering characteristic clues for serious skin adverse reactions.
- This study thoroughly described the characteristics of SJS/TEN related to PD-1/PD-L1 inhibitors usage, such as latency period, severity, and clinical outcomes.
- This study provides a reference for further research on the incidence and pathogenesis of SJS/TEN associated with PD-1/PD-L1 inhibitors usage.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

RQC collected data and drafted the initial manuscript. THX designed the project and edited the discussion. Both authors contributed to important editorial changes of important content in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the institutional research ethics committee of Hangzhou Third People's Hospital (approval file number: 2024KA106). The procedure for obtaining patients' informed consent has been exempted by the ethics committee of Hangzhou Third People's Hospital.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

Arranz-Nicolás J, Martin-Salgado M, Adán-Barrientos I, Liébana R, Del Carmen Moreno-Ortíz M, Leitner J, et al. Diacylglycerol kinase α inhibition cooperates with PD-1-targeted therapies to restore the T cell activation program. Cancer Immunology, Immunotherapy. 2021; 70: 3277–3289. https://doi.org/10.1007/s00262-021-02924-5

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. The Journal of Investigative Dermatology. 2000; 115: 149–153. https://doi.org/10.1046/j.1523-1747.2000.00061.x

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Archives of Dermatology. 1993; 129: 92–96.

Berner F, Bomze D, Diem S, Ali OH, Fässler M, Ring S, et al. Association of Checkpoint Inhibitor-Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non-Small Cell Lung Cancer. JAMA Oncology. 2019; 5: 1043–1047. https://doi.org/10.1001/jamaoncol.2019.0402

Cartotto R, Mayich M, Nickerson D, Gomez M. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. Journal of Burn Care & Research. 2008; 29: 141–146. https://doi.org/10.1097/BCR.0b013e320083865

Chen PY, Li ZY, Cai SQ. Case Report: Cadonilimab-related toxic epidermal necrolysis-like reactions successfully treated with supplemental Adalimumab. Frontiers in Immunology. 2023; 14: 1188523. https://doi.org/10.3389/fimmu.2023.1188523

Chen W, Huang Y, Pan W, Xu M, Chen L. Strategies for developing PD-1 inhibitors and future directions. Biochemical Pharmacology. 2022; 202: 115113. https://doi.org/10.1016/j.bcp.2022.115113

Cheng B, Xiao Y, Xue M, Cao H, Chen J. Recent Advances in the Development of PD-L1 Modulators: Degraders, Downregulators, and Covalent Inhibitors. Journal of Medicinal Chemistry. 2020; 63: 15389–15398. https://doi.org/10.1021/acs.jmedchem.0c01362

Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. Current Problems in Cancer. 2017; 41: 125–128. https://doi.org/10.1016/j.currproblcancer.2016.12.001

Goldinger SM, Stieger P, Meier B, Micaletto S, Contassot E, French LE, et al. Cytotoxic Cutaneous Adverse Drug Reactions during Anti-PD-1 Therapy. Clinical Cancer Research. 2016; 22: 4023–4029. https://doi.org/10.1158/1078-0432.CCR-15-2872

Hu CH, Chang NJ, Liu EKW, Chuang SS, Chung WH, Yang JY. SCORTEN and impaired renal function related to mortality of toxic epidermal necrolysis syndrome patients in the Asian population. Journal of the European Academy of Dermatology and Venereology. 2012; 27: 628–633. https://doi.org/10.1111/j.1468-3083.2012.04502.x

Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. JAMA Dermatology. 2016; 152: 45–51. https://doi.org/10.1001/jamadermatol.2015.2707

Huang Y, Soon YY, Aminkeng F, Tay SH, Ang Y, Kee ACL, et al. Risk factors for immune-related adverse events from anti-PD-1 or anti-PD-L1 treatment in an Asian cohort of nonsmall cell lung cancer patients. International Journal of Cancer. 2021; 150: 636–644. https://doi.org/10.1002/ijc.33822

Jiang Y, Chen M, Nie H, Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. Human Vaccines & Immunotherapeutics. 2019; 15: 1111–1122. https://doi.org/10.1080/21645515.2019.1571892

Johnson DB, Chandra S, Sosman JA. Immune Checkpoint Inhibitor Toxicity in 2018. JAMA. 2018; 320: 1702–1703. https://doi.org/10.1001/jama.2018.13995

Kruger S, Ilmer M, Kobold S, Cadilha BL, Endres S, Ormanns S, et al. Advances in cancer immunotherapy 2019 - latest trends. Journal of Experimental & Clinical Cancer Research. 2019; 38: 268. https://doi.org/10.1186/s13046-019-1266-0

Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clinical Reviews in Allergy & Immunology. 2017; 54: 147–176. https://doi.org/10.1007/s12016-017-8654-z

Li G, Gong S, Wang N, Yao X. Toxic epidermal necrolysis induced by sintilimab in a patient with advanced non-small cell lung cancer and comorbid pulmonary tuberculosis: A case report. Frontiers in Immunology. 2022; 13: 989966. https://doi.org/10.3389/fimmu.2022.989966

Li X, Li G, Chen D, Su L, Wang RP, Zhou Y. Case Report: sintilimab-induced Stevens-Johnson Syndrome in a patient with advanced lung adenocarcinoma. Frontiers in Oncology. 2023; 13: 912168. https://doi.org/10.3389/fonc.2023.912168

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981; 30: 239–245. https://doi.org/10.1038/clpt.1981.154

Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. The New England Journal of Medicine. 2018; 378: 158–168. https://doi.org/10.1056/NEJMra1703481

Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. The New England Journal of Medicine. 1995; 333: 1600–1607. https://doi.org/10.1056/NEJM199512143332404

Sibaud V. Dermatologic Reactions to Immune Checkpoint Inhibitors: Skin Toxicities and Immunotherapy. American Journal of Clinical Dermatology. 2017; 19: 345–361. https://doi.org/10.1007/s40257-017-

0336-3

Sohrabi C, Mathew G, Maria N, Kerwan A, Franchi T, Agha RA, et al. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. International Journal of Surgery. 2023; 109: 1136–1140. https://doi.org/10.1097/JS9.0000000000000373

Vivar KL, Deschaine M, Messina J, Divine JM, Rabionet A, Patel N, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. Journal of Cutaneous Pathology. 2017; 44: 381–384. https://doi.org/10.1111/cup.12876

Yang H, Ma Q, Sun Y, Zhang K, Xing Y, Li H. Case Report: Toxic epidermal necrolysis associated with sintilimab in a patient with relapsed thymic carcinoma. Frontiers in Oncology. 2022; 12: 1065137. https://doi.org/10.3389/fonc.2022.1065137

Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Molecular Cancer. 2022; 21: 28. https://doi.org/10.1186/s12943-021-01489-2

Yoest JM. Clinical features, predictive correlates, and pathophysiology of immune-related adverse events in immune checkpoint inhibitor treatments in cancer: a short review. ImmunoTargets and Therapy. 2017; 6: 73–82. https://doi.org/10.2147/ITT.S126227

Zhang L, Wu Z. Adalimumab for Sintilimab-Induced Toxic Epidermal Necrolysis in a Patient with Metastatic Gastric Malignancy: A Case Report and Literature Review. Clinical, Cosmetic and Investigational Dermatology. 2023; 16: 457–461. https://doi.org/10.2147/CCID.S401286

Zhao X, Bao Y, Meng B, Xu Z, Li S, Wang X, et al. From rough to precise: PD-L1 evaluation for predicting the efficacy of PD-1/PD-L1 blockades. Frontiers in Immunology. 2022; 13: 920021. https://doi.org/10.3389/fimmu.2022.920021

Ziemer CM, Miedema J, Smith CJ, Liu Z, Thomas NE, Googe PB. Immunohistochemical Expression of PD-L1 Is Increased in Lesional Epidermal Keratinocytes in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. The American Journal of Dermatopathology. 2021; 43: 318–320. https://doi.org/10.1097/DAD.0000000000001816

Zou W, Luo X, Gao M, Yu C, Wan X, Yu S, et al. Optimization of cancer immunotherapy on the basis of programmed death ligand-1 distribution and function. British Journal of Pharmacology. 2023; 181: 257–272. https://doi.org/10.1111/bph.16054