

Steven-Johnson Syndrome: A Rare but Serious Adverse Event of Nivolumab Use in a Patient With Metastatic Gastric Adenocarcinoma

Eltaib Saad^{a, c}, Pabitra Adhikari^a, Drashti Antala^a, Ahmed Abdulrahman^a, Valiko Begiashvili^a, Khalid Mohamed^a, Elrazi Ali^b, Qishou Zhang^a

Abstract

Nivolumab is a humanized monoclonal anti-programmed cell death receptor-1 (PD-1) antibody that has been authorized for use in the treatment of advanced malignancies. Cutaneous reactions are the most common immune-related adverse events reported with anti-PD-1 agents, and they range broadly from mild localized reactions to rarely severe or life-threatening systemic dermatoses. The occurrence of Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) with nivolumab use is an exceedingly rare phenomenon that was only documented in a handful of cases in the current literature, but it deserves careful attention as SJS/TEN may be associated with fatal outcomes. We present a case of nivolumab-induced SJS/TEN in a middle-aged female patient with metastatic gastric adenocarcinoma that was successfully treated with immunosuppressive therapy and supportive care. Prompt recognition of SJS/TEN with discontinuation of nivolumab is warranted when SJS/TEN is suspected clinically. Multidisciplinary management in a specialized burn unit is the key to improving outcomes of SJS/TEN.

Keywords: Anti-programmed cell death receptor-1 agents; Cutaneous adverse reactions; Immune checkpoint; Nivolumab; Steven-Johnson syndrome; Rare

Introduction

Anti-programmed cell death receptor-1 (anti-PD-1) agents have been increasingly used for the treatment of advanced malignancies in modern oncology practice [1, 2]. Anti-PD-1

agents have positively impacted the outcome of some metastatic cancers with substantial improvement in the life expectancy of the affected patients [1, 2]. Anti-PD-1 agents are targeted monoclonal antibodies against certain immune checkpoint molecules in the signaling of downstream cascades of inflammatory and immune pathways (such as programmed cell death-1 (PD-1) receptors or their ligands (PD-L1) and cytotoxic T lymphocytes-associated antigen-4 (CTLA-4) [3].

Numerous immune-related adverse events (irAEs) have emerged with the recent use of these novel agents due to the disturbance of the physiological pathways that maintain a state of peripheral immune tolerance [3], with the cutaneous reactions being considered the most frequent adverse events described with immune checkpoint inhibitors [1, 2]. The cutaneous irAEs range considerably from mild localized reactions that are relatively common and largely manageable (including, for instance, pruritis, lichenoid reactions, maculopapular rashes, and granulomatous skin disorders) to rare systemic conditions that may be associated with serious or life-threatening outcomes like Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [1, 2, 4]. Although yet to be completely understood, SJS/TEN is believed to be a drug-related cytotoxic reaction that induces massive apoptosis of keratinocytes [5].

Herein, we present a case of SJS/TEN in a middle-aged female patient with metastatic gastric adenocarcinoma after treatment with nivolumab. A comprehensive literature review was conducted to summarize all the published cases of nivolumab-associated SJS/TEN.

Case Report

Investigations

A 45-year-old female with a past medical history of gastric adenocarcinoma with hepatic and bony metastasis (proximal humeral and iliac metastatic diseases) presented to the emergency department for evaluation of skin rash. The patient reported a rash on the right shoulder and the right upper extremity that progressed to involve her torso and lower extremities with the development of painful blisters over a course of 1 week. She denied fevers, rigors, sore throat, eye swelling or discharge, fatigue, nausea, vomiting, diarrhea, or joint swelling.

Manuscript submitted August 2, 2022, accepted August 24, 2022

Published online September 28, 2022

^aDepartment of Internal Medicine, Ascension Saint Francis Hospital, Evanston, IL, USA

^bDepartment of Internal Medicine, One Brooklyn Health, Interfaith Medical Center, Brooklyn, NY, USA

^cCorresponding Author: Eltaib Saad, Department of Internal Medicine, Ascension Saint Francis Hospital, Evanston, IL, USA.

Email: eltaib.saad@ascension.org

doi: <https://doi.org/10.14740/jmc3992>

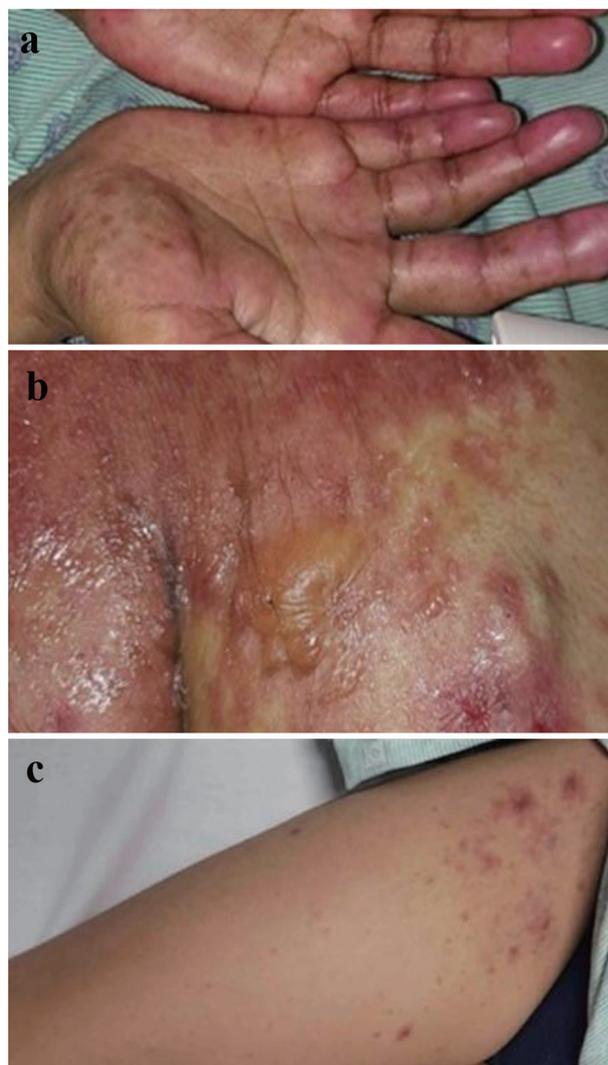


Figure 1. (a) A confluent papular rash over both hands. (b) Erupted rash with vesicles and bullae over the right shoulder. (c) A maculopapular rash over the right upper extremity.

The patient had received three cycles of nivolumab and five cycles of FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin), with the last dose of nivolumab administered 2 weeks prior to the onset of skin rash. The patient also received radiation therapy to the right hip, right shoulder, and left thigh 1 week prior to index presentation. The patient was not known to have a known drug allergy. No use of Chinese medicines or herbal supplements (CAM) was reported by the patient.

General examination revealed a toxic-looking patient who was afebrile (temperature of 37 °C), tachypneic (respiratory rate of 24 breaths/min), hypotensive to 85/55 mm Hg, and tachycardic to 110 beats/min. The physical examination was notable for diffuse skin rash with various evolution stages, including confluent maculopapular rash with scattered erosions, sloughing, and crusts, alongside vesicles and hyperpigmented plaques involving lips and oral mucosa, bilateral hands (Fig. 1a), right shoulder (Fig. 1b), right upper extremity (Fig. 1c), thighs, and

Table 1. Pertinent Laboratory Results on Admission

Blood test	Patient's result	Reference result
Venous lactate	2.1 mmol/L	0.6 - 2.1 mmol/L
Serum bicarbonate	14.0 mmol/L	21.0 - 28.0 mmol/L
Serum anion gap	10.0 mmol/L	6.0 - 14.0 mmol/L
Serum creatinine	1.30 mg/dL	0.6 - 1.30 mg/dL
Serum sodium	130 mmol/L	133 - 144 mmol/L
Serum chloride	99 mmol/L	98 - 107 mmol/L
Serum potassium	4.6 mmol/L	3.5 - 5.2 mmol/L
Blood urea	23.0 mg/dL	8.6 - 25.0 mg/dL
Serum magnesium	1.4 mg/dL	1.5 - 2.6 mg/dL
Serum phosphate	4.1 mg/dL	2.5 - 4.5 mg/dL
Serum uric acid	6.9 mg/dL	4.4 - 7.6 mg/dL
Hemoglobin	9.5 g/dL	13.0 - 15.0 g/dL
Platelets	103 × 10 ³ /mm ³	150 - 450 × 10 ³ /mm ³
White blood cell	1.8 × 10 ³ /mm ³	4.0 - 11.0 × 10 ³ /mm ³
Serum albumin	3.8 g/dL	3.5 - 5.7 g/dL
Procalcitonin	0.60 ng/mL	0.20 - 0.49 ng/mL

gluteal region. Approximately 15% of total body surface area (BSA) demonstrated skin eruption with a positive Nikolsky sign. Table 1 summarizes relevant laboratory results (with reference ranges) on admission.

Diagnosis

At this point, the differential diagnosis included radiation-induced dermatitis exacerbated by an immune checkpoint inhibitor (i.e., nivolumab), SJS/TEN overlap, or drug rash secondary to 5-fluorouracil or oxaliplatin. However, the confluent nature of the eruptive rash, evidence of bullae and vesicles, presence of mucocutaneous lesions, and involvement of areas that were not subjected to radiotherapy, e.g., hands and feet strongly favor a diagnosis of SJS/TEN. Nivolumab was discontinued given the clinical suspicion of SJS/TEN overlap.

A skin biopsy of one of the right upper extremity lesions revealed focal full-thickness necrosis of the epidermis, interface dermatitis, mild perivascular mixed inflammatory cell infiltrate with eosinophils in the dermis, and diffuse subepidermal splitting confirming a final diagnosis of SJS. A clinical diagnosis of SJS/TEN overlap was considered based on the total BSA involved by the erupted rash. Calculated SCORTEN was 4 (age > 40 years, associated malignancy, affected TBS > 10%, and serum bicarbonate < 20 mmol/L) which was associated with a 58.3% mortality rate.

Treatment

A multidisciplinary team, including critical care, oncology, dermatology, nutritional services, and burn teams was in-

Table 2. Common Cutaneous irAEs Reported in 253 Patients^a Treated With Various Anti-PD-1 Agents per Review Conducted by Simonsen et al [1]

Cutaneous irAE	Patients number	Time to onset from the last cycle of anti-PD-1 agents (weeks)
Pigmentation changes/vitiligo	58	1 - 36
Psoriasis	33	2 - 22
Bullous pemphigoid	31	3 - 84
Lichenoid dermatitis	30	< 1 - 92
Granulomatous reactions	10	4 - 40
Erythema multiforme/SJS/TEN	10	< 1 - 20
Lupus erythematosus-like rash	8	4 - 43

^aSix patients had more than one specific skin reaction. irAEs: immune-related adverse effects; SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis; anti-PD-1: anti-programmed cell death receptor-1.

involved in patient care given the predicated fatal outcome of SJS/TEN overlap. The patient was admitted to a specialized burn intensive care unit (ICU) and started on prednisone at 1 mg/kg daily, which was tapered when the rash improved to grade 1 dermatitis (evident by faint erythema, regression of skin involvement to < 10% BSA, and minimal pain). The patient was commenced on topical steroids given the possibility of radiation dermatitis. Critical supportive care with hydration, nutritional supplements, adequate analgesia, and standard wound care was provided.

Follow-up

The patient's rash continued to improve with gradual healing of the erupted skin. She was discharged with closed outpatient follow-up with oncology and dermatology services.

Discussion

Immune checkpoint molecules (such as PD-1 and CTLA-4) are essentially inhibitory regulators that serve to maintain a physiological state of immune tolerance against self-antigens in the peripheral tissues by attenuating the cytotoxic effects of immune cells through complex signaling pathways [6]. The expression of CTLA-4 on the regulatory T cells in the lymphoid organs during the priming phase primarily mediates an overall inhibitory effect on the cellular immune system [6]. PD-1 is a receptor expressed on the activated B cells and T cells; the interaction between PD-1 and their ligands (PD-L1) prevents autoimmunity by mediating an inhibitory effect on the effector cells through the suppression of T cells activation against self-antigens in the periphery [7]. However, PDL-1 is overexpressed by tumor cells and the tumor microenvironment (TME) to escape themselves from the host immune system via attenuation of effector T cells' activities against tumor cells [6, 7].

Anti-PD1 agents are immune checkpoint inhibitors that block the interactions between PD-1 and PD-L1, resulting in the promotion of activated T cells to enhance their intrinsic ant-tumor effects, and thus suppressing tumor growth [6, 7]. Nevertheless, an exaggerated response to the latter T cells ac-

tivation may also trigger a loss of self-tolerance, eventually accumulating in the occurrence of irAEs [8].

irAEs encompass a broad spectrum of various organ-specific syndromes (i.e., cutaneous reactions, arthritis, colitis, pneumonitis, thyroiditis, and hypophysitis) [1, 3, 6-8] with different grades of severity that are classified according to the criteria of Common Terminology of Adverse Events (CTAEs) [9]. It was estimated that almost half of patients (49%) treated with anti-PD-1 agents had developed cutaneous irAEs [10], accounting for the most frequently reported irAEs [10].

A wide range of cutaneous irAEs were described in the literature that appeared after varied latency periods of exposure to anti-PD-1 therapy [1, 3, 6]. Fortunately, the majority of skin reactions were of mild grades (grade I and II) that were either self-limiting or relatively manageable [1]. Table 2 summarizes the common cutaneous adverse events described in 253 patients who were treated with various anti-PD-1 agents in a review conducted by Simonsen et al [1]. Pigmentary changes/vitiligo were the most frequent cutaneous irAEs (58 patients), followed by psoriasis, bullous pemphigoid, and lichenoid dermatitis (33, 31, and 30 patients, respectively) [1].

The exact mechanisms of cutaneous irAEs remain poorly understood [1, 6]. Several theories were postulated to explain the pathophysiology of immune checkpoint inhibitors-induced skin toxicities [2, 3]. The most plausible theory is the presumed exaggerated response of effector T cells, which results in cytotoxic and inflammatory damage to cutaneous and subcutaneous tissues, partly because of the blockade of inhibitory PD-1/PD-L1 effects [8]. Dual use of an anti-CTLA-4 blocker with an anti-PD-1 agent increases the risk of irAEs [8]. Furthermore, combination therapy with anti-PD-1 agents was associated with both a higher risk of occurrence of cutaneous irAEs and a worsening clinical profile of skin toxicities (grade III and VI), as demonstrated from the phase III trial of augmented ipilimumab-plus-nivolumab therapy to treat metastatic melanoma [11].

The occurrence of severe systemic cutaneous irAEs such as SJS/TEN is a clinical rarity [2, 4]. An extensive review published by Maloney et al [4] identified a total of 18 patients with SJS/TEN following treatment with different anti-PD-1 agents (pembrolizumab, ipilimumab, nivolumab, and atezolizumab) [4]. We conducted a comprehensive search to identify nivolumab-induced SJS and/or TEN cases (either as a mono-

therapy or combination therapy), which yielded 11 patients [12-22]. One patient was managed with dual therapy with ipilimumab, and one was treated with nivolumab after the failure of ipilimumab. Table 3 outlines baseline patient characteristics, latency onset, the clinical presentation of SJS/TEN, and outcome and management for each patient. Seven cases were SJS, while TEN was diagnosed in three cases [12, 13, 15], and one case was an SJS/TEN overlap in keeping with our reported patient [17].

SJS/TEN rash onset ranged from 1 week [16, 20] to 4 months [14] with an average latency of 2 - 4 weeks. Interestingly, in the latter case [14], SJS rash appeared after eight cycles of nivolumab therapy in a similar pattern of delayed autoimmune diseases [14]. Furthermore, compared to other medications such as lamotrigine when SJS manifested within the first few days of drug exposure [4], a relatively long latency of nivolumab-induced SJS (few weeks) is observed, and this finding may be explained by the different pharmacokinetics profile of nivolumab which reaches the steady-state concentration after 12 weeks with a half-life of 25 days [23]. The lack of prodromal symptoms in our patient is in line with the reviewed literature that reported constitutional symptoms in three cases only [16, 17, 19].

Recall radiation dermatitis in association with SJS/TEN observed in the presented patient was described in similar two cases that were pre-medicated with radiotherapy [20, 21], and this phenomenon of the distinct distribution of rash over previous radiation sites may be related to a selective re-exposure of certain epitopes from radiation-damaged skin cells to locally hyperactive T cells [20].

SJS/TEN management entails a multidisciplinary team (critical care, dermatology, oncology, and infectious diseases) with an integral component of supportive care, preferably in a specialized burn unit for standard care of skin wounds [24]. Optimization of fluid balance, correction of electrolytes/micronutrient disturbances, and aggressive sepsis source control is necessary to minimize associated morbidities [24]. Early recognition of SJS/TEN with immediate discontinuation of the offending agent (nivolumab) is essential to avoid the further dissemination of rash [14]. Nivolumab was the likely culprit of SJS in our case, as the calculated Naranjo algorithm was 7 which denotes a probable association [25] (Table 4). No trials of nivolumab rechallenge after SJS/TEN diagnosis were attempted in the available literature [4]. Immunosuppressive therapy with systemic steroids was associated with better outcomes of SJS, as all the seven cases of nivolumab-induced SJS (without TEN) had survived [14, 16, 18-22]. Furthermore, a recent meta-analysis has reported a beneficial role for cyclosporin (CsA) in SJS/TEN management, as CsA may block the cytotoxic T cells-induced epithelial cell injury [26]. TEN was associated with much worse mortality rates as all four patients with TEN died from polymicrobial sepsis and progression of the underlying malignancies [12, 13, 15, 17].

Conclusion

The authors described a rare case of nivolumab-induced SJS/TEN in a patient with metastatic gastric adenocarcinoma that

was successfully managed with immunosuppressive therapy and supportive care. Prompt clinical recognition of SJS/TEN, early discontinuation of nivolumab, and multidisciplinary management with critical supportive care in a specialized burn unit have contributed to the reasonable clinical recovery of our patient. A high index of clinical suspicion is warranted to identify SJS/TEN in patients treated with anti-PD-1 agents as SJS/TEN.

Learning points

The occurrence of SJS or TEN with nivolumab use is an exceedingly rare phenomenon that yet deserves serious attention due to the possible fatal outcomes associated with SJS/TEN.

Physicians should be aware of severe cutaneous adverse effects of anti-PD-1 agents, especially with their increasing use in modern oncology practice.

Early recognition of SJS/TEN and prompt discontinuation of nivolumab are warranted when SJS/TEN is suspected clinically.

Multidisciplinary management (involving critical care, nutrition services, dermatology, oncology, and infectious diseases) is essential to improving the outcome of SJS/TEN.

Acknowledgments

The authors would like to acknowledge the Department of Intensive Care Unit at Saint Francis Presence Hospital for providing valuable input to this case presentation.

Financial Disclosure

The authors confirm that there is no funding to declare regarding the publication of this case report.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Informed Consent

Informed written consent was obtained from the patient to write and publish their case as a case report with all accompanying clinical images.

Author Contributions

ES, PA, and DA contributed to conceptualizing and writing the first manuscript. AA, VB, KM, EA, and QZ contributed to editing the final draft. ES and DA performed the critical review. All authors were involved in the clinical management

Table 3. A Literature Review of the Published Cases of Nivolumab-Induced SJS/TEN

Authors, year of publication	Patient's age (years/gender)	Underlying malignancy	Latency of onset of SJS/TEN symptoms	Management	Outcome of SJS/TEN
Vivar et al, 2017 [12]	50/male	Metastatic malignant melanoma treated with dual anti-PD-1 agents (ipilimumab and nivolumab)	Initial clinical and pathological findings were consistent with a morbilliform drug rash which then progressed over 3 months to clinicopathological TEN. SCORTEN 5.	Poor response to infliximab and oral prednisone, followed by high-dose methylprednisolone and immunoglobulins	Lack of response of cutaneous lesions to immunosuppressive therapy with global clinical condition's decline from polymicrobial sepsis. Death from multiorgan failure.
Kim et al, 2021 [13]	86/male	Metastatic HCC	Mucocutaneous lesions appeared after 14 days of the second cycle. Histology confirmed TEN. SCORTEN 3, mortality rate 35.5%.	Failure of oral prednisone. ICU admission with high-dose methylprednisolone and immunoglobulins	Initial re-epithelialization of some skin lesions but overall clinical course deteriorated due to polymicrobial sepsis and advanced HCC. Death from multiorgan failure.
Dasanu, 2019 [14]	69/male	Metastatic HCC status post resection and recurrent tumor arterial embolization	Late onset of mucocutaneous lesions after 4 months (eight cycles) of nivolumab. Histology confirmed SJS.	Oral prednisone and supportive care	Complete resolution of mucocutaneous lesions within 3 weeks of treatment
Griffin et al, 2018 [15]	54/male	Recurrent follicular lymphoma	Mucocutaneous lesions appeared after 10 days of the first cycle. Histology confirmed TEN. SCORTEN 3, mortality rate 32%.	High-dose methylprednisolone followed by oral prednisone and supportive care	Initial rash improvement followed by TEN of respiratory mucosa, hospital-acquired cases of pneumonia leading to progressive respiratory failure and death
Garcia-Canzana et al, 2021 [16]	78/male	Metastatic SCC lung	Mucocutaneous lesions and constitutional symptoms 1 week after the second cycle. Histology confirmed SJS.	High-dose methylprednisolone followed by oral prednisone with tapering, and supportive care	Complete disappearance of mucocutaneous lesions after 1 month
Koshizuka et al, 2021 [17]	76/male	Metastatic SCC tongue status post resection and neck dissection, radiotherapy, and chemotherapy	Cutaneous lesions appeared after 27 days of the first cycle followed by the constitutional symptoms. Histology confirmed SJS. TEN was clinically diagnosed later in the second week of symptoms onset.	High-dose methylprednisolone followed by oral prednisone with gradual tapering and supportive care	Gradual improvement of rash with epithelialization of the erupted lesions
Ito et al, 2017 [18]	76/female	Stage IV NSCLC	The unspecified onset of cutaneous lesions after the second cycle. SJS was complicated by refractory pruritis. Histology confirmed SJS.	Oral prednisone for 2 weeks and a topical steroid with supportive care	Complete disappearance of the rash but refractory pruritis that was, interestingly, aprepitant-responsive.
Salati et al, 2018 [19]	59/female	Metastatic NSCLC status post chemotherapy	Mucosal lesions and constitutional symptoms 1 week after the second cycle followed by a diffuse eruptive rash.	High-dose methylprednisolone and supportive care	Gradual rash improvement and skin healing
Shah et al, 2018 [20]	63/male	Stage IV SCC of uvula and soft palate status post neck dissection and local radiotherapy	Mucosal and cutaneous lesions appeared after 1 week after the first cycle. Skin rash distributed over recent radiation sites. Histology confirmed SJS.	Supportive care only	Good outcome of SJS rash
Rouyer et al, 2018 [21]	63/male	Recurrent pulmonary epidermoid carcinoma status post palliative radiotherapy and immunotherapy	Oral mucositis after 5 days from the second cycle and cutaneous lesions after 2 weeks, the rash appeared over previous radiation sites. Histology confirmed SJS with recall radiation dermatitis.	Unspecified	Unspecified
Nayar et al, 2016 [22]	64/female	Metastatic malignant melanoma refractory to ipilimumab therapy	Initial morbilliform rash that appeared after 2 weeks from the second cycle of nivolumab. The rash progressed into diffuse eruptive rash over 2 weeks with histology confirmed SJS.	High-dose methylprednisolone and immunoglobulins initially, followed by cyclosporin and oral prednisone taper	Gradual improvement of the skin rash.

HCC: hepatocellular carcinoma; SCC: squamous cell carcinoma; NSCLC: non-small cell lung carcinoma; SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis; anti-PD-1: anti-programmed cell death receptor-1; ICU: intensive care unit.

Table 4. Calculated Adverse Drug Reaction Probability Scale (Naranjo Algorithm) in Our Case [25]

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	+1
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				+7

Total score ≥ 9 : definite. 5 - 8: probable. 1 - 4: possible. ≤ 0 : doubtful.

of the reported patient. All authors agreed to the final draft submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Simonsen AB, Kaae J, Ellebaek E, Svane IM, Zachariae C. Cutaneous adverse reactions to anti-PD-1 treatment-A systematic review. *J Am Acad Dermatol.* 2020;83(5):1415-1424.
2. Chen CH, Yu HS, Yu S. Cutaneous adverse events associated with immune checkpoint inhibitors: a review article. *Curr Oncol.* 2022;29(4):2871-2886.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* 2018;378(2):158-168.
4. Maloney NJ, Ravi V, Cheng K, Bach DQ, Worswick S. Stevens-Johnson syndrome and toxic epidermal necrolysis-like reactions to checkpoint inhibitors: a systematic review. *Int J Dermatol.* 2020;59(6):e183-e188.
5. Fakoya AOJ, Omenyi P, Anthony P, Anthony F, Etti P, Otohinyi DA, Olunu E. Stevens - Johnson syndrome and toxic epidermal necrolysis; extensive review of reports of drug-induced etiologies, and possible therapeutic modalities. *Open Access Maced J Med Sci.* 2018;6(4):730-738.
6. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov.* 2018;8(9):1069-1086.
7. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, et al. Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* 2015;33(18):2004-2012.
8. Guo L, Zhang H, Chen B. Nivolumab as programmed death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. *J Cancer.* 2017;8(3):410-416.
9. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol.* 2017;28(10):2377-2385.
10. Hwang SJ, Carlos G, Wakade D, Byth K, Kong BY, Chou S, Carlino MS, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. *J Am Acad Dermatol.* 2016;74(3):455-461.e451.
11. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(1):23-34.
12. Vivar KL, Deschaine M, Messina J, Divine JM, Rabionet A, Patel N, Harrington MA, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. *J Cutan Pathol.* 2017;44(4):381-384.
13. Kim MC, Khan HN. Nivolumab-Induced Toxic Epidermal Necrolysis: Rare but Fatal Complication of Immune Checkpoint Inhibitor Therapy. *Cureus.* 2021;13(5):e15017.
14. Dasanu CA. Late-onset Stevens-Johnson syndrome due to nivolumab use for hepatocellular carcinoma. *J Oncol Pharm Pract.* 2019;25(8):2052-2055.
15. Griffin LL, Cove-Smith L, Alachkar H, Radford JA, Brooke R, Linton KM. Toxic epidermal necrolysis (TEN) associated with the use of nivolumab (PD-1 inhibitor) for lymphoma. *JAAD Case Rep.* 2018;4(3):229-231.
16. Gracia-Cazana T, Padgett E, Calderero V, Oncins R. Nivolumab-associated Stevens-Johnson syndrome in a patient with lung cancer. *Dermatol Online J.* 2021;27(3):13.
17. Koshizuka K, Sakurai D, Sunagane M, Mita Y, Hamasaki S, Suzuki T, Kikkawa N, et al. Toxic epidermal necrolysis

- associated with nivolumab treatment for head and neck cancer. *Clin Case Rep.* 2021;9(2):848-852.
18. Ito J, Fujimoto D, Nakamura A, Nagano T, Uehara K, Imai Y, Tomii K. Aprepitant for refractory nivolumab-induced pruritus. *Lung Cancer.* 2017;109:58-61.
 19. Salati M, Pifferi M, Baldessari C, Bertolini F, Tomasello C, Cascinu S, Barbieri F. Stevens-Johnson syndrome during nivolumab treatment of NSCLC. *Ann Oncol.* 2018;29(1):283-284.
 20. Shah KM, Rancour EA, Al-Omari A, Rahnema-Moghadam S. Striking enhancement at the site of radiation for nivolumab-induced Stevens-Johnson syndrome. *Dermatol Online J.* 2018;24(6):7.
 21. Rouyer L, Bursztejn AC, Charbit L, Schmutz JL, Moawad S. Stevens-Johnson syndrome associated with radiation recall dermatitis in a patient treated with nivolumab. *Eur J Dermatol.* 2018;28(3):380-381.
 22. Nayar N, Briscoe K, Fernandez Penas P. Toxic epidermal necrolysis-like reaction with severe satellite cell necrosis associated with nivolumab in a patient with ipilimumab refractory metastatic melanoma. *J Immunother.* 2016;39(3):149-152.
 23. Sheng J, Srivastava S, Sanghavi K, Lu Z, Schmidt BJ, Bello A, Gupta M. Clinical pharmacology considerations for the development of immune checkpoint inhibitors. *J Clin Pharmacol.* 2017;57(Suppl 10):S26-S42.
 24. Lemiale V, Meert AP, Vincent F, Darmon M, Bauer PR, Van de Louw A, Azoulay E, et al. Severe toxicity from checkpoint protein inhibitors: What intensive care physicians need to know? *Ann Intensive Care.* 2019;9(1):25.
 25. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.
 26. Ng QX, De Deyn M, Venkatanarayanan N, Ho CYX, Yeo WS. A meta-analysis of cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Inflamm Res.* 2018;11:135-142.