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Case Report
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Management of Fatal Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN) as Immune Checkpoint Inhibitor-Associated Cutaneous Toxic: Case Report and Literature Review

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Abstract

Background: Immune Checkpoint Inhibitors (ICIs) have made significant progress in anti-tumor therapy and are increasingly applied in clinical treatment. Immunotherapy-related Adverse Events (irAEs) are a major concern when ICIs are used clinically. As a severe form of skin toxicity, fatal Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) is relatively rare in clinical practice, there are no reports of SJS/TEN caused by Tirelizumab. For the treatment of SJS/TEN, various combinations of antibiotics, immunosuppressive and glucocorticoid agents are used.

Case Report: We report a case of critical SJS/TEN in an adult lung squamous cell carcinoma patient who was undergoing immune checkpoint blockade with Tirelizumab, a Programmed cell Death-1 (PD-1) receptor inhibitor. The patient presented with fever, pain, anemia, rash with ulcers all over the body, myocardial injury, reduced T-lymphocytes activity and elevated IL-6 levels. Our patient was successfully treated by a multi-modality therapy regimen based on glucocorticoids.

Conclusion: Our report demonstrates that severe rash is an important marker of abnormal immune status, which is followed by varying degrees of multiple organ dysfunction. Myositis is the most dangerous adverse event, closely related to the prognosis of patients. Early identification, multi-departmental consultation, and high-dose corticosteroids are the keys to successful treatment of such patients.

Keywords: Stevens-Johnson Syndrome (SJS); Toxic Epidermal Necrolysis (TEN); Immunotherapy-related adverse events; Tirelizumab

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Background

Immune Checkpoint Inhibitors (ICIs) are human-derived monoclonal antibodies that enhance the anti-tumor immune response of T cells by inhibiting the Programmed cell Death-1 (PD-1)/ Programmed Death-Ligand-1 (PD-L1) pathway, thus producing anti-tumor immune effects. Tirelizumab is a PD-1 antibody inhibitor that has been shown to be effective in combination with chemotherapy for the treatment of squamous cell lung cancer, however, the subsequent immunotherapy-related Adverse Events (irAEs) have also been widely observed. It has been reported that among patients receiving anti-PD-1/PD-L1 therapy, about 70% had at least one irAE, 10% had severe irAEs, and 0.5% had fatal irAEs [1].

Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) is a severe type of pleomorphic erythema and a rare adverse mucocutaneous reaction with a mortality rate of up to 50% [2,3]. The Body Surface Area of the skin (BSA) is the main criterion to distinguish SJS and TEN: BSA<10% is classified as SJS, BSA>30% is classified as TEN, and BSA in between is classified as overlapping type SJS/TEN [4]. The main clinical manifestations of this disease are skin blisters,

bullae, epidermal exfoliation, mucosal erosion, etc., and in severe cases, there are systemic poisoning symptoms and different degrees of involvement of internal organs [5]. Because of the difficulty in conducting randomized controlled trials in patients with such critical diseases, the standardized treatment of SJS/TEN is a major clinical challenge. The mainstream treatment measures include immediate discontinuation of suspected allergenic drugs, wound care and drug therapy. Although systemic application of glucocorticoids is currently the most common treatment method, some studies have shown that the use of high-dose glucocorticoids increases the risk of complications [6]. Other treatments such as Intravenous Immunoglobulin (IVIG), immunosuppressants, plasma exchange, etc., although clinically found to improve the condition to a certain extent, but there is no definite study to prove that it can effectively reduce the mortality of the disease [7].

Therefore, there is an urgent need for new and effective treatments to improve the prognosis of the disease. In this report, we described the case of a patient with lung squamous cell carcinoma in whom multiple immune-related adverse events were induced by Tirelizumab.

Case Presentation

An adult patient with lung squamous cell carcinoma was admitted to the hospital with 7-day history of high fever (up to 104.2 degrees Fahrenheit), pain, nausea and rash 17 days after receiving 2 doses of Tirelizumab (200 mg). Initial workup revealed anemia (hemoglobin level, 9.7 g/dL [normal: 13 to 17 g/dL]) with low red blood cell count (2.99×10^{12}/L [normal: 4 to 5.5 $\times 10^{12}$/L]). Elevated creatine kinase isoenzyme (169.0 U/L [normal: 0 to 24 U/L]), myoglobin (78.7 μg/L [normal: 8 to 20 μg/L]), highly sensitive troponin (14.15 pg/ml [normal: 0 to 0.04 pg/ml]). Hypokalemia (3.25 mmol/L [normal: 3.5 to 5 mmol/L]), the detection of Th1. Th2. Th17 cell subsets suggested increased expression of IL-6 and TNF-α. Lymphocyte subsets detection suggested a decrease in the absolute count of T lymphocytes, CD4+ T lymphocytes, and CD8+ T lymphocytes. Extensive lab and radiologic work up to identify any infectious agents was unremarkable.

After a Multidisciplinary Team (MDT) consultation including

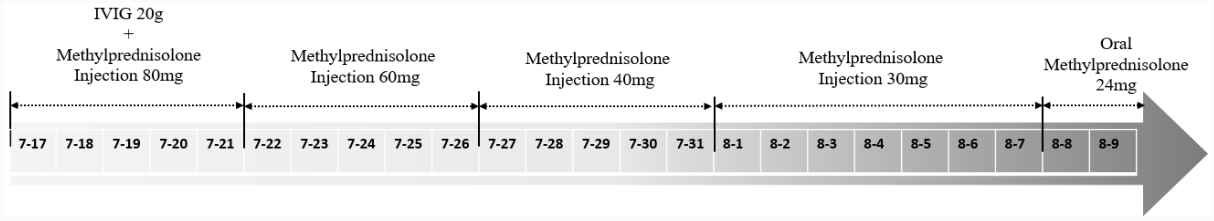

Figure 1: The application process of IVIG and glucocorticoids.

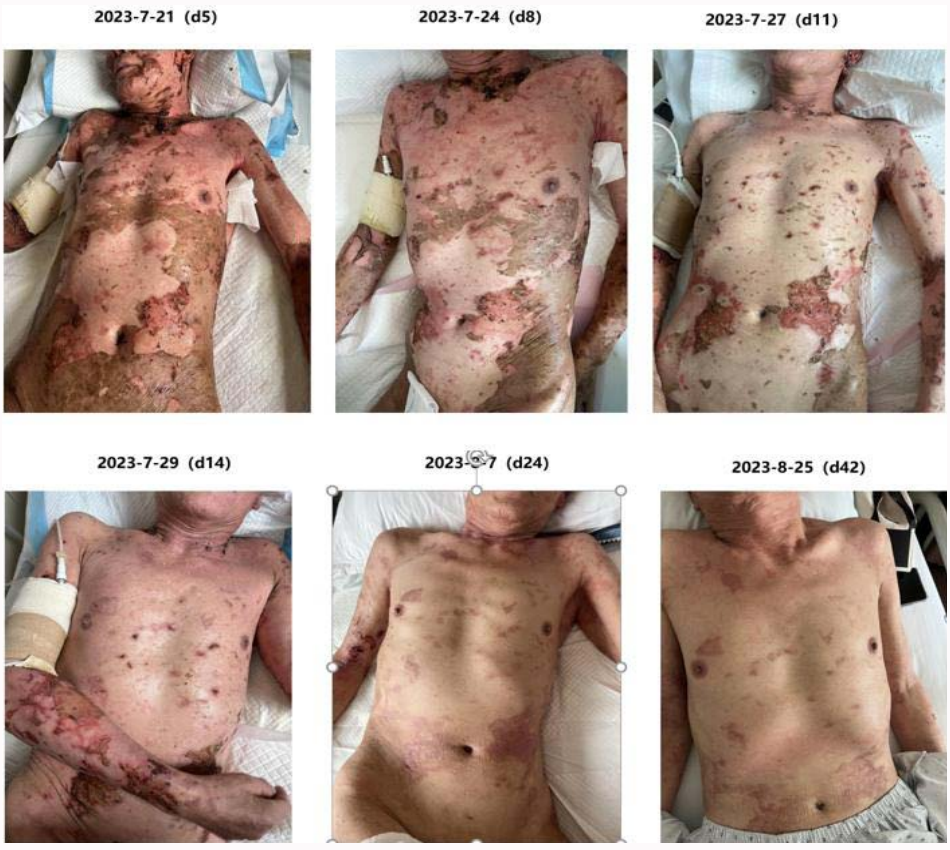

Figure 2: The skin toxicity eventually disappeared after 42 days of treatment.

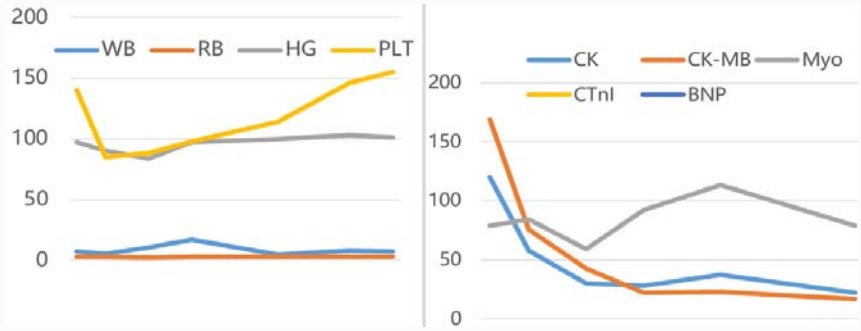

Figure 3: Laboratory inspection basically return to normal.

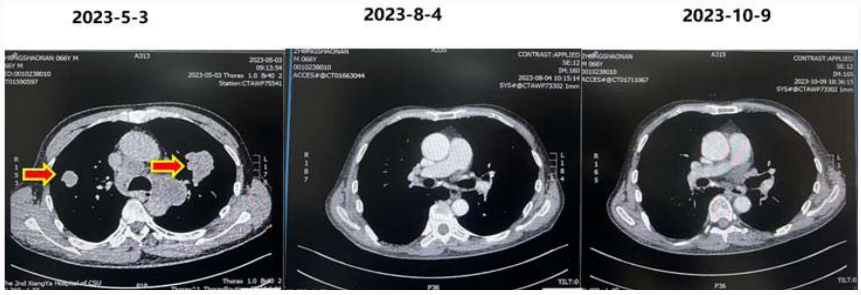

Figure 4: The lung mass disappeared and remained stable during the subsequent 5-month evaluation.

Table 1: Literature review of TNF-α inhibitors in the treatment of SJS/TEN.

Medication	References	Case	Outcome (mortality rate)
Etanercept Single	Bakir 2021 [17]	1	cure
	Paradise 2020 [20]	17	11.8%
	Torres-Navarro [18]	4	cure
	Eliades [21]	4	cure
Combined with glucocorticoid	Shen 2020 [22]	1	cure
	Wang 2019 [23]	1	cure
Combined with IVIG	Pham 2019 [24]	13	not mentioned
Combined with glucocorticoid and IVIG	Holtz 2021 [16]	1	cure
	Sibbald 2020 [25]	1	not mentioned
	Estébanez 2020 [26]	1	cure
Infliximab Single	Chafranska 2019 [27]	1	cure
	Wallenborn 2017 [28]	1	cure
Combined with glucocorticoid	Jiang 2018 [29]	1	cure
	Vivar 2017 [30]	1	cure

department of oncology, nutrition, dermatology, infection, pharmacy, burns and plastic surgery, integrated traditional Chinese and western medicine, Intensive Care Unit (ICU), the patient was treated with high-dose glucocorticoids (2 mg per kilogram per day), intravenous immunoglobulin (1 g per kilogram per day) (Figure 1), apply compound tung leaf burn oil to the skin around the body, Norfloxacin cream and Vaseline gauze to the skin ulcer, maintain skin temperature by infrared irradiation, protect mucous membrane by recombinant human epidermal growth factor, and supportive treatments such as anti-infection, nutritional support, and maintenance of water-electrolyte balance.

After 22 days of treatment, the dermatologic toxicities were gradually alleviated, and then, oral prednisone was gradually reduced. The treatment lasted for 42 days, and the skin toxicity eventually disappeared (Figure 2). The relevant indicators of laboratory inspection basically return to normal (Figure 3). In terms of lung carcinoma, the lung mass disappeared and remained stable during the subsequent 5-month evaluation (Figure 4).

Discussion and Conclusion

The mechanism of irAEs induced by anti-PD-1/PD-L1 therapy is mainly due to the overactivation of the immune system. Activated T cells can not only bind specifically to tumor-associated antigen epitopes to exert anti-tumor effects, but also attack normal tissues containing common epitopes of tumor-associated antigens, thus causing targeted autoimmune toxicity. SJS/TEN is an immune

disease dominated by delayed type hypersensitivity on the basis of genetic predisposition [8]. Immunohistochemical studies showed that the epidermis of SJS/TEN lesions was mainly infiltrated by CD8+ T cells, and CD8+ Cytotoxic T Cells (CTL) and Natural Killer cells (NK) infiltrated the blister fluid and epidermis in the early stage of the disease [9]. CTL and NK cells induce apoptosis of keratinocytes by activating the Caspase cascade through the apoptosis-associated Factor (Fas)-Fas Ligand (FasL) pathway; in addition, CTL and NK cells directly or indirectly induce apoptosis and necrosis of keratinocytes by secreting cytotoxic proteins such as granzyme B, perforin, and granzyme A [10]. Interestingly, a large number of cytokines of different types can be detected in both peripheral blood and local skin lesions of patients at both early and late stages of the disease, which not only amplify the cascade effect of inflammation, but also directly participate in the necrosis and apoptosis of epithelial cells. Therefore, "cytokine storm" is considered to be the most important factor leading to rapid progression of the disease, and also one of the causes of damage to various internal organs [11]. The cytokines related to SJS/TEN mainly include Tumor Necrosis Factor (TNF)-α, Interferon (IFN)-γ, Interleukin (IL)-6, IL-15, IL-12 and IL-18, etc. Among them, TNF-α, IL-15 and IL-6 are particularly important [12-14].

There is no standard treatment regimen for SJS/TEN. MDT is particularly important in the management of critical SJS/TEN. By applying high dose corticosteroids combined with IVIG early can rapidly arrest SJS, while the optimal cutoff time of corticosteroids remains controversial because of its adverse drug reaction [15]. In our case, the patient attended an MDT consultation including department of oncology, nutrition, dermatology, infection, pharmacy, burns and plastic surgery, integrated traditional Chinese and western medicine, ICU. Finally, the patient achieved good results under multidisciplinary treatment.

In addition to corticosteroids and IVIG, drugs that suppress the immune response or inflammatory factors are also being tried in the treatment of SJS/TEN. Several studies have demonstrated the effectiveness of TNF-α inhibitors Etanercept and Infliximab in the treatment of SJS/TEN [16-19]. Summary of previously reported TNF-α inhibitor treatment for SJS/TEN is shown in Table 1. It is believed that the effectiveness and safety of such drugs for SJS/TEN will eventually be more rigorously confirmed.

SJS/TEN is a rare serious adverse event of immunotherapy, and its high mortality has seriously affected the use and development of ICIs in cancer patients. Our case indicates that the combination of high-dose corticosteroid shock therapy, IVIG, and best supportive care might reduce mortality in the treatment of SJS/TEN. However, there is still a long way to go in terms of how to prevent SJS/TEN and how to manage the disease more scientifically.

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References

1. Jing Y, Zhang YC, Wang J, Li K, Chen X, Heng J, et al. Association between sex and immune-related adverse events during immune checkpoint inhibitor therapy. J Natl Cancer Inst. 2021;113(10):1396-404.
2. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: From science to translation. J Dermatol Sci. 2020;98(1):2-12.
3. Chaby G, Maldini C, Haddad C, Lebrun-Vignes B, Hemery F, Ingen-Housz-Oro S, et al. Incidence of and mortality from epidermal necrolysis (Stevens-Johnson syndrome/toxic epidermal necrolysis) in France during 2003-16: A four-source capture -recapture estimate. Br J Dermatol. 2020;182(3):618-24.
4. White K D, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: Building multidisciplinary networks to drive science and translation. J Allergy Clin Immunol Pract. 2018;6(1):38-69.
5. Tsai TY, Huang IH, Chao YC, Li H, Hsieh TS, Wang HH, et al. Treating toxic epidermal necrolysis with systemic immunomodulating therapies: A systematic review and network meta-analysis. J Am Acad Dermatol. 2021;84(2):390-97.
6. Yang L, Shou YH, Li F, Zhu XH, Yang YS, Xu JH. Retrospective study of 213 cases of Stevens -Johnson syndrome and toxic epidermal necrolysis from China. Burns. 2020;46(4):959-69.
7. Zhang C, Zhu Z, Gao J, Yang L, Dang E, Fang H, et al. Plasma exosomal miR-375-3p regulates mitochondria-dependent keratinocyte apoptosis by targeting XIAP in severe drug-induced skin reactions. Sci Transl Med. 2020;12(574):6142.
8. Chung WH, Wang CW, Dao RL. Severe cutaneous adverse drug reactions. J Dermatol. 2016;43(7):758-66.
9. Tohyama M, Watanabe H, Murakami S, Shirakata Y, Sayama K, Iijima M, et al. Possible involvement of CD14 + CD16 + monocyte lineage cells in the epidermal damage of Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2012;166(2):322-30.
10. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14(12):1343-50.
11. Gao X, Tang X, Ai L, Gao Q, Liao Q, Chen M, et al. Acute pancreatic injuries: A complication of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with cytotoxic immunocell activation. J Am Acad Dermatol. 2021;84(3):644-53.
12. Wang CW, Yang LY, Chen CB, Ho HC, Hung SL, Yang CH, et al. Randomized, controlled trial of TNF-α antagonist in CTL-mediated severe cutaneous adverse reactions. J Clin Invest. 2018;128(3):985-96.
13. Ao S, Gao X, Zhan J, Ai L, Li M, Su H, et al. Inhibition of tumor necrosis factor improves conventional steroid therapy for Stevens -Johnson syndrome/toxic epidermal necrolysis. J Am Acad Dermatol. 2022,86(6):1236-45.
14. Shiohara T, Mizukawa Y, Aoyama Y. Monitoring the acute response in severe hypersensitivity reactions to drugs. Curr Opin Allergy Clin Immunol. 2015;15(4):294-9.
15. Lehloenya RJ, Isaacs T, Nyika T, Dhana A, Knight L, Veenstra S, et al. Early high-dose intravenous corticosteroids rapidly arrest Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms recurrence on drug re-exposure. J Allergy Clin Immunol Pract. 2021;9:582-4.
16. Holtz M, Grimstad F, Higgins J, Denny G, Strickland J, Dowlut-McElroy T. Vulvovaginal involvement in pediatric Stevens-Johnson syndrome: A case series. J Pediatr Adolesc Gynecol. 2021;34(5):745-8.
17. Bakir M, Almeshal H, Alturki R, Obaid S, Almazroo A. Toxic epidermal necrolysis post COVID-19 vaccination first reported case. Cureus. 2021;13(8):e17215.
18. Torres-Navarro I, Briz-Redon A, Botella-Casas G, Sahuquillo-Torralba A, Calle-Andrino A, de Unamuno-Bustos B, et al. Accuracy of SCORTEN and ABCD-10 to predict mortality and the influence of renal function in Stevens-Johnson syndrome/toxic epidermal necrolysis. J Dermatol. 2020;47(10):1182-6.
19. Kumar R, Bhandari S. Pembrolizumab induced toxic epidermal necrolysis. Curr Probl Cancer. 2020;44(2):100478.
20. Paradisi A, Abeni D, Didona D, Ricci F, Canzona F, Didona B. A new

case series on etanercept treatment for toxic epidermal necrolysis. Eur J Dermatol, 2020;30(5):561-8.

21. Eliades P, Fonseca M, Harp J. Use of etanercept in a series of pediatric patients with Stevens-Johnson syndrome-toxic epidermal necrolysis spectrum disease. JAMA Dermatol. 2020;156(8):921-2.

22. Shen MH, Liu MT, Chung WH, Lu CW. Toxic epidermal necrolysis induced by human herpesvirus 7 treated with a tumor necrosis factor-α inhibitor. J Dermatol. 2020;47(10):1179-81.

23. Wang F, Gao X, Chen X, Tang X, Chen H, Han J. Successful treatment of interstitial lung disease related to Stevens-Johnson syndrome/toxic epidermal necrolysis overlap with etanercept: A case report and published work review. J Dermatol. 2019;46(11):10358.

24. Pham CH, Gillenwater TJ, Nagengast E, McCullough MC, Peng DH, Garner WL. Combination therapy: Etanercept and intravenous immunoglobulin for the acute treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis. Burns. 2019;45(7):1634-8.

25. Sibbald C, Putterman E, Micheletti R, Treat J, Castelo-Soccio L. Retrospective review of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis cases at a pediatric tertiary care institution. Pediatr Dermatol. 2020;37(3):461-6.

26. Estébanez A, S5ez-Martn LC, Muoz JI, Silva E, Monrabal A, Monteagudo C, et al. Levetiracetam-induced pediatric toxic epidermal necrolysis successfully treated with etanercept. Pediatr Dermatol. 2020;37(4):701-5.

27. Chafranska L, Saunte DM, Behrendt N, Nygaard U, Christensen RJ, Sand C, et al. Pediatric toxic epidermal necrolysis treated successfully with infliximab. Pediatr Dermatol. 2019;36(3):342-5.

28. Wallenborn J, Fischer M. Intensive care in a patient with toxic epidermal necrolysis. Case Rep Crit Care. 2017;2017:3246196.

29. Jiang YY, Nguyen GH, Jin HZ, Zeng YP. Methazolamide-induced toxic epidermal necrolysis in a man carrying HLA-B*59:01: Successful treatment with infliximab and glucocorticoid. Int J Dermatol. 2018;57(4):494-6.

30. 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. J Cutan Pathol. 2017;44(4):381-4.