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CASE REPORT

Case Report: Pirfenidone-Induced Toxic Epidermal Necrolysisa a Rare Idiosyncratic Reaction

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Abstract: Toxic epidermal necrolysis (TEN) is a rare and low incidence rate disease characterized by pirfenidone-induced skin damage. Pirfenidone is a new anti-fibrotic and anti-inflammatory drug that can alleviate the deterioration of lung function in patients with COVID-19-induced pneumonia and prolong the progression-free survival period. However, side effects of pirfenidone have drawn widespread attention, which include gastrointestinal symptoms, liver damage, skin photosensitivity, and rash. So far, many cases caused by pirfenidone have been reported. As far as we know, cases of TEN induced by pirfenidone have rarely been reported. This article presents cases of TEN induced by pirfenidone, so that clinicians can be aware of the possibility of TEN when using pirfenidone, and how to use inflammation-relevant indicators for evaluating the severity and risk of death of TEN, which has potential clinical value.

Keywords: toxic epidermal necrolysis, pirfenidone, inflammation relevant indicators, clinical value

Introduction

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a severe skin and mucous membrane reaction with a high risk of death. It is mostly caused by drugs and is characterized by bullae and generalized epidermolysis, accompanied by a series of systemic symptoms, including multiple organ dysfunction syndrome. At present, SJS and TEN represent a group of diseases, SJS is light (epidermolysis size < 10% body surface area), TEN for heavy (epidermolysis area > 30% body surface area), type in between to overlap SJS - TEN (epidermolysis area of 10%~30% body surface area). SJS/TEN is relatively rare, with an annual reported incidence rate of (1–7)/million.[1] In the severe acute stage of the disease, SJS/TEN is accompanied by a series of systemic symptoms, and results in in-hospital death in 12–49% of cases.[2]

Case Presentation

An 84-year-old Chinese man was a patient of COVID-19 pathogenic pneumonia. He has a history of hypertension and diabetes and stays in the hospital for one month. This patient has idiopathic pulmonary fibrosis and has been receiving pirfenidone treatment. In the first week, 0.2g each time, 3 times a day; In the second and third weeks, 0.4g each time, three times a day; In the 4th week, 0.6g each time, 3 times a day. After taking pirfenidone for 28 days, the patient developed red maculopapular rashes on the chest, accompanied by itching and pain upon touch, which gradually spread throughout the body. The patient immediately discontinued pirfenidone. Following, he took "Desloratadine Tablets" at a dose of 10mg per day on his own. However, the rash did not improve. After 5 days, bullies appeared on his back and limbs, and there was erosion and exudation on his lips and scrotum, with significant pain and elevated body temperature. Therefore, he came to our hospital for treatment (Figure 1a–d). Laboratory testing revealed perturbations in inflammation. White blood cell count: 9.7×10^9/L, neutrophil count: 7.0×10^9/L, red blood cell count: 4.11×10^{12}/L, hemoglobin

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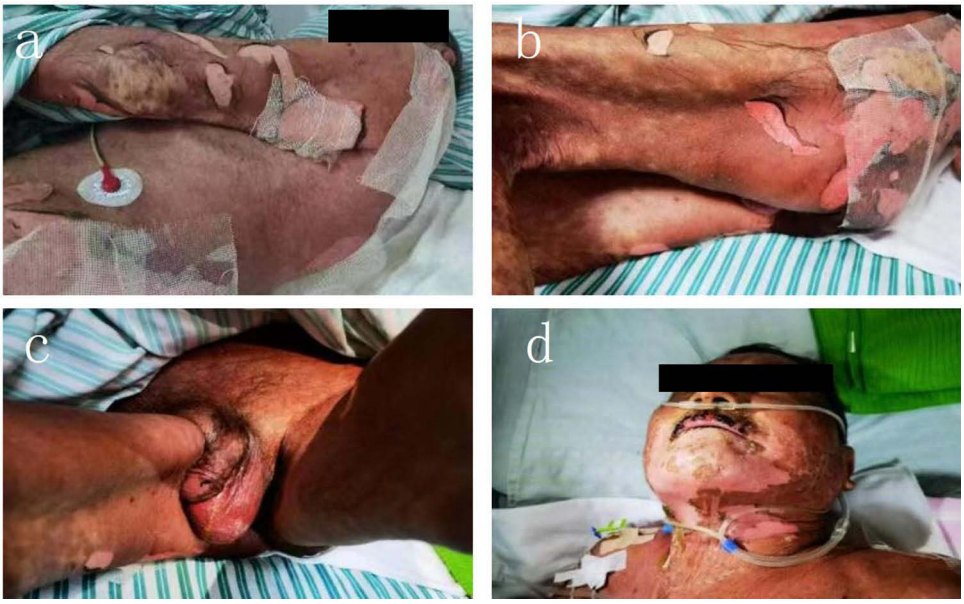

Figure 1 Physical examination 48 h after the onset of skin symptoms. (**a** and **b**) Visible bullae appeared on the limbs and the trunk; (**c**) There is a clear inflammatory reaction in the scrotum: erosion and exudation; (**d**) There is a clear inflammatory reaction in the lip: erosion and exudation.

quantity: 127g/L, platelet count: 175×10^9/L, C-reactive protein: 74.79mg/L; Lactate dehydrogenase: 309U/L, Glucose: 8.2mmol/L; Prothrombin time: 12.9 seconds, International normalized ratio: 1.22, D-dimer: 1590μg/L. A chest CT scan shows two cases of pneumonia. In addition, we found large bullae with loose walls, clear surfaces, and disintegration of the epidermis during the physical examination. The affected area covered 50% of the body, and Nikolsky's sign was positive. The patient was given an intravenous drip of methylprednisolone at a dose of 40mg twice a day, human albumin 5g each time, once a day, intravenous drip. Three days later, the rash still increased. Human immunoglobulin 22g was added once a day. After five days, the skin lesions improved without new bullae. Later, the skin lesions all over the body dried up and peeled off.

In order to clarify the correlation between pirfenidone and SIS/TEN, we referred to the Naranjo's adverse reaction (ADR) evaluation Scale (Table 1), which indicates that the association between pirfenidone and severe skin damage according to the classification criteria of the National Cancer Institute's Common Adverse Event Evaluation Criteria

Table 1 Naranjo's Adverse Reaction (ADR) Evaluation Scale

Relevant Issues	Score		
	Yes	No	Unknown
1. Are there previous conclusive reports on this reaction?	+1	0	0
1. Did the adverse event appear after the suspected drug was administered?	+2	−1	0
1. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
1. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0
1. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
1. Did the reaction reappear when a placebo was given?	−1	+1	0
1. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
1. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0

(*Continued*)

Table 1 (Continued).

Relevant Issues	Score		
	Yes	No	Unknown
1. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total scores	**6**		

Note: A total score ≥ 9 is affirmative. A score 5 to 8 is very likely. 1 to 4 points possible; ≤0 points suspicious.

(NCI-CTCAE) version 5.0. In addition, to monitor the risk of death, new inflammatory markers were used to assess the mortality rate of patients with TEN in SCORTEN (Severity-of-Illness Score for Toxic Epidermal Necrolysis), which includes C-reactive protein-albumin ratio (CAR); prognostic nutritional index (PNI); red blood cell distribution width-to-albumin ratio (RAR); and Neutrophil-lymphocyte ratio (NLR) (Figure 2 and Table 2). In this case report, we dynamically monitored the changes in inflammatory-related biomarkers. NLR and RAR obviously increased and reached the peak on day 2023–03-21, then the levels of NLR and RAR began to decline. However, the level of PNI began to significantly increase from day 2023–03-21 to 2023–04-7. It is particularly important to note that CAR shows a different trend from the existing research.

Discussion

SJS/TEN are mainly drug-induced diseases. The most frequently causative drugs include antiepileptic drugs/mood stabilizers (carbamazepine, dilantin, phenobarbital, oxcarbazepine); antibiotics (sulfonamides, penicillins, cephalosporins, Quinolones, minocycline); allopurinol; non-steroidal anti-inflammatory drug (Oxicams, Arylacetic acids, Coxibs) and nevirapine ect;[3,4] Relatively rare causative drugs include antitubercular agent (Isoniazide, rifampicin); Other antibiotics (chloramphenicol, vancomycin, teicoplanin, clindamycin); proton pump inhibitor; antiviral agent; antidepressant; gout suppressant, and anti-tumor drugs/immunomodulators ect.[3,4] Regarding treatment, cyclosporine is the most effective therapy for the treatment of SJS, and a combination of intravenous immunoglobulin (IVIg) and corticosteroids is most effective for SJS/TEN overlap and TEN. The combined use of cyclosporine can reduce the occurrence of systemic infection and accelerate epithelial reformation.[5,6]

The pathogenesis of TEN involves a complex immune cascade reaction, mediated by the interaction between the particulate protein and Fas ligand, resulting in extensive keratinocyte apoptosis and subsequent extensive epidermal necrosis.[7] SJS/TEN is distinctive by the activation of cytotoxic T-cell type 1 (Tc1) and natural killer (NK) cells,

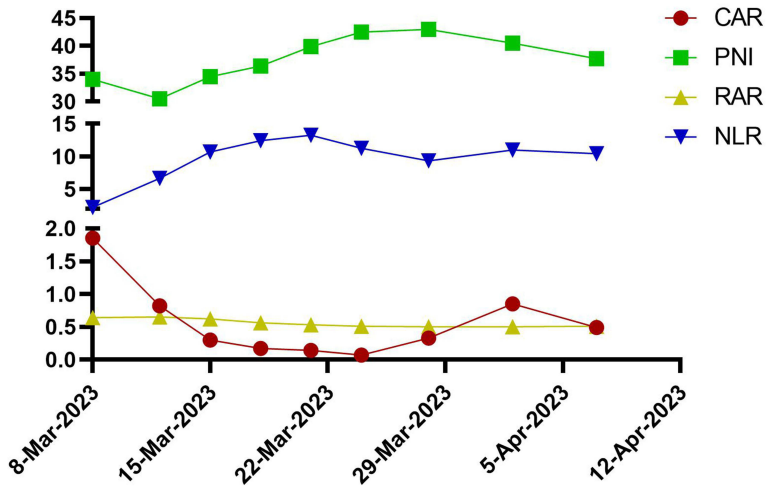

Figure 2 Dynamic changes in the severity and risk of death factors for TEN patient induced by pirfenidone.

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Table 2 Dynamic Changes in the Severity and Risk of Death Factors for TEN Patient Induced by Pirfenidone

Date	CAR	PNI	RAR	NLR
2023-03-08	1.85	34.0	0.64	2.21
2023-03-12	0.82	30.5	0.65	6.67
2023-03-15	0.30	34.5	0.62	10.67
2023-03-18	0.17	36.4	0.56	12.40
2023-03-21	0.14	39.9	0.53	13.25
2023-03-24	0.07	42.5	0.51	11.25
2023-03-28	0.33	43.0	0.50	9.33
2023-04-02	0.85	40.5	0.50	11.00
2023-04-07	0.49	37.7	0.51	10.43

corresponding to hypersensitivity reaction type IVc.[8] Tc1 expresses FasL after recognizing antigens presented by human leukocyte antigen (HLA) cells, releasing cytotoxic molecules such as granulysin (GNLY), granzyme B (GZMB), and perforin (PRF1) from its granules, causing cutaneous and mucosal necrosis.[9]

Epidemiological investigations have found that SJS/TEN is a relatively rare disease with a low incidence rate and a high fatality rate. The SCORTEN (Severity-of-Illness Score for Toxic Epidermal Necrolysis) is a validated assessment tool used to estimate the likelihood of in-hospital death for patients with TEN.[10] To be mentioned, new inflammatory-related markers were used to assess the mortality rate of patients with TEN in SCORTEN, which indicates the role of biomarkers in predicting the severity of TEN and the risk of death.[10] Inflammation Relevant indicators: CAR; PNI; RAR; and NLR are considered to be related to the severity of the disease and the prognosis of patients. Elevated levels of CAR and NLR are associated with an increased risk of death from TEN. It will be a reliable prognostic indicator and inflammatory marker for the severity of TEN.[2,11] RAR is an indicator that can simultaneously reflect the degree of inflammatory response and nutritional status.[12] PNI is based on serum albumin (ALB) and the total number of peripheral blood lymphocytes. The calculated results are closely related to systemic immunity, inflammation, and nutritional status.[13] Relative reports have demonstrated that PNI was negatively correlated with the severity and mortality of TEN. Elevated PNI level was a protective factor for death.[14] In this case report, we found the dynamic tendency of new inflammatory biomarkers was consistent with the patient's course of illness.

Among the four markers, NLR and RAR can partially reflect severity and inflammatory status in patients with TEN. NLR was also a predictor of death. In univariate analysis, RAR > 0.46 was associated with an increased risk of patient mortality, while PNI > 36.50 was a protective factor for SJS/TEN.[14,15] In this case, we observed that the value of RAR reached its peak at the onset of the disease, and then continued to decline as the infection duration increased. Although it did not drop below 0.46, the risk of death significantly decreased. At the same time, we also found that the value of PNI has been above 36.4 from 2024–03-21, and the risk of patient death has significantly decreased. The disease development trend that reacted to these biomarkers was consistent, and the patients eventually recovered and were discharged from the hospital. Inflammation Relevant indicators, including CAR, PNI, RAR, and NLR, are important indicators for evaluating the severity and risk of death of SJS/TEN, which has potential clinical value.

Conclusion

Here, we report on a rare pirfenidone-induced TEN case, involving new inflammatory-related markers in the prediction of the mortality risk of patients with TEN. This case advances our understanding of pirfenidone treatment-induced skin photosensitivity of adverse effects. Furthermore, TEN has a relatively high risk of patient mortality, and using inflammatory-related biomarkers to assess the progression of a patient's condition has potential clinical value.

Consent Statement

The patient had given written informed consent for the publication of his clinical details and accompanying images. Institutional approval is not required for this case study.

Disclosure

The authors have no relevant financial or non-financial interests to disclose in this work.

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