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CASE REPORT

Integrated Glucocorticoids and Traditional Chinese Medicine in a Squamous Lung Cancer Patient with Dermatologic Toxicities Related to Pembrolizumab: A Case Report

Yu Yi Chen[1–3,*], Tongtong Wu[4,*], Guowang Yang[4], Jie Yu[4]

[1]State Key Laboratory of Traditional Chinese Medicine Syndrome, The second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, People's Republic of China; [2]Chinese Medicine Guangdong Laboratory, Hengqin, Guangdong, People's Republic of China; [3]Postdoctoral Research Workstation, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, People's Republic of China; [4]Department of Oncology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guowang Yang; Jie Yu, Department of Oncology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, No. 23, Back Road of Art Gallery, Dongcheng District, Beijing, 100010, People's Republic of China, Email guowang_yang@163.com; Jie_Yu2024@163.com

Abstract: The report presents the case of a 70-year-old man with advanced squamous lung cancer who developed dermatologic toxicities after receiving Pembrolizumab-based therapy. During the acute phase, the patient was treated with an integrative treatment of glucocorticosteroids and traditional Chinese medicine (TCM) and achieved superior efficacy. The patient presented with blisters and papules distributed covering 60% of the trunk and extremities, along with more than 90% coverage of the hands and feet, graded as a cutaneous immune-related adverse event (irAE) of 3–4 levels, and accompanied by pruritus, infections, hypercoagulation, hypoproteinemia, and electrolyte disturbance. He was initially on intravenous glucocorticoids synchronized with TCM decoctions for seven days, which effectively intercepted the appearance of fresh cutaneous lesions, with noticeable alleviation of pruritus and other complications. He then began to taper his glucocorticoid dosage with the assistance of TCM. Antihistamines and topicals were used in the first three weeks. As a result, the cutaneous symptoms were well controlled, and he was subsequently transferred for further anti-tumor therapies. In conclusion, integrated glucocorticoids and TCM was used to bring the patient out of the acute phase of high-grade irAE dermatologic toxicity successfully. In this case, the cutaneous symptoms were resolved more rapidly, with earlier glucocorticoid tapering and fewer adverse hormonal effects, without tumor progression.

Keywords: immune-related adverse event, irAE, traditional Chinese medicine, TCM, dermatologic toxicity, case report

Introduction

Squamous cell carcinoma is one of the common pathological types of non-small cell lung cancer (NSCLC),[1] with persistently high mortality.[2] The limited response in advanced squamous lung cancer is attributed to its exclusion from targeted therapies. Notably, Pembrolizumab plus chemotherapy was demonstrated in the KEYNOTE-407 trial[3] to achieve an absolute benefit of 5.6 months in median overall survival (mOS), becoming a decisive favorable factor for efficacy at a 0.59 hazard ratio. However, the activated cytotoxic T lymphocytes are likely to attack normal organs by blocking the same immune checkpoints (ICIs),[4,5] Wherein, dermatologic irAEs are the most prevalent,[6] manifested as maculopapular rash, pruritus, bullous dermatitis, etc.[7] Although the dermatologic toxicities above grade 3 occur in only 1%~3%, these high-grade cases typically require hospitalization and discontinuation of ICIs, which has been proven to reduce the subjects' long-term survival outcomes significantly.[8,9] Moreover, it cannot be ignored the poor quality of life (QoL) from cutaneous symptoms, disability risk, and feelings of stigmatization by society.[10]

A glucocorticoid regimen at 0.5–2mg/kg/day until cutaneous symptoms improve to grade 1 has already been recommended by the National Comprehensive Cancer Network (NCCN). Also, its adverse events, like ulcers or Cushing's phenotype, should

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be taken into account when prescribing, especially in the elderly.[11] Besides, glucocorticoids are recognized to reshape tumor immune microenvironment (TIME), for instance, via inhibiting inflammation alarming, stimulating T cell polarizing toward T_H2 and regulatory T cell, alternatively activating M2c-type macrophage.[12] It remains controversial whether these anti-inflammatory pathways will assist immune escape and enrich the risk of tumor progression.[13] Thus, a strategy on dermatologic irAEs is needed for balancing immune evocation and suppression.

Traditional Chinese medicine (TCM) can improve efficacy against malignancies[14] through immune checkpoints,[15,16] and also act as immune regulators on cutaneous symptoms.[17] We present an advanced squamous lung cancer case who developed high-grade dermatologic toxicities after the Pembrolizumab and benefited from the integrated glucocorticoids and TCM.

Case Presentation

The publication of the case report was approved by the patient and his authorized relative, with signed informed consent. CARE (CAse REport) guidelines were followed in the preparatory process.

A 70-year-old male patient with advanced squamous cell lung cancer (T4N2–3M0, IIIB) developed mild generalized pruritus after six cycles of chemo-immunotherapy (pembrolizumab 200mg on day 1, paclitaxel (albumin-bound) 500mg on day 1, carboplatin 600mg on day 1, every 21 days; adjusting subsequent two cycles because of myelosuppression after cycle 4: pembrolizumab 200mg on day 1, paclitaxel (albumin-bound) 400mg on day 1, carboplatin 400mg on day 1, every 21 days) and three cycles of immuno-maintenance therapy (pembrolizumab 200mg on day 1, every three weeks). However, rather than suspending the immunotherapy and controlling the skin symptoms, he insisted on receiving the next cycle of pembrolizumab on the sixth day after the itching began. He subsequently suffered from an extensive rash with intense itching, which progressively worsened until it became unbearable one month later despite the administration of loratadine and the application of mometasone furoate cream and halometasone cream.

When the patient was transferred to our hospital, blisters and papules were extensively distributed on the patient's trunk and extremities, covering over 60% of the body surface area (BSA) (Figure 1). These lesions were irregular and above the epidermis, with alternating scratches, ulcers, and crusts. Even worse, the skin of both hands and feet was swollen and tight, with over 90% coverage of blisters, papules, and yellowish bloody secretions where the epidermis had peeled off. The rash was accompanied by persistent itching and intermittent mild pain, leading to severe limitations in his daily life, especially insomnia and difficulties in walking or gripping. Penicillin- and erythromycin-resistant Staphylococcus aureus was incubated

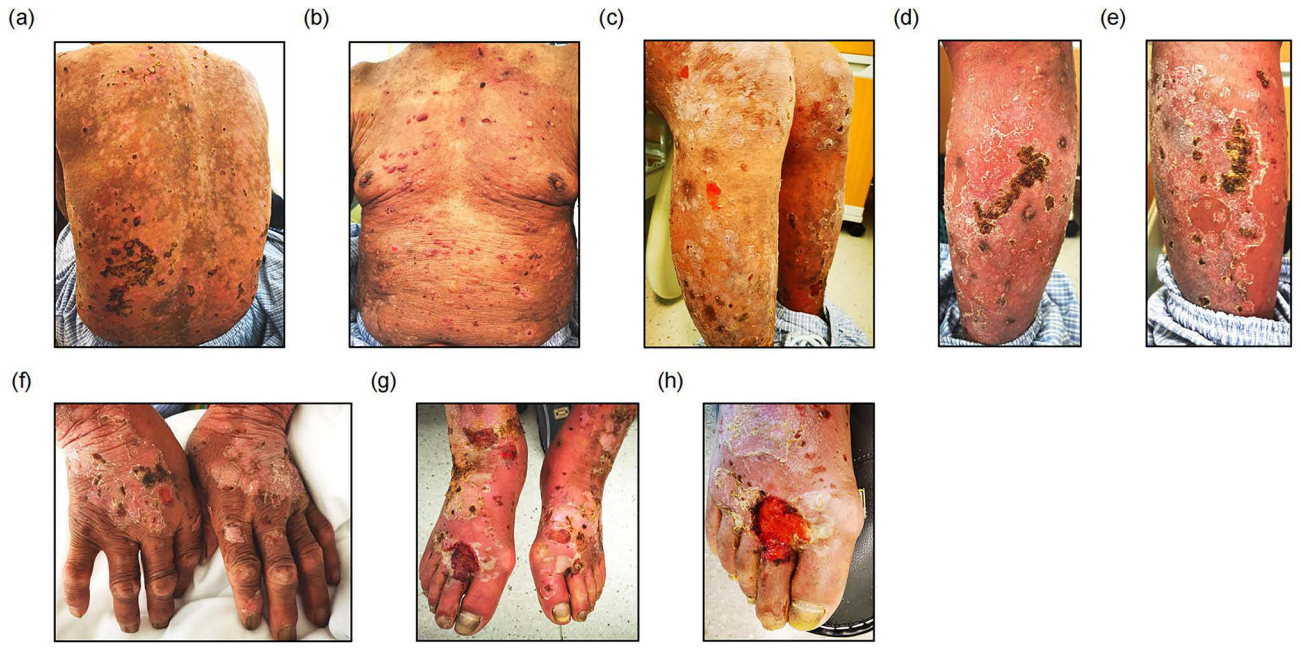

Figure 1 Skin lesions on hospital day 1. (**a**) back; (**b**) chest and abdomen; (**c**) front of calves; (**d**) back of the right calf; (**e**) back of the left calf; (**f**) backs of the hands; (**g**) backs of the feet; (**h**) magnification of the ulcer on the right dorsal foot.

from the ulcer secretions, with increased eosinophil ratio and elevated C-reactive protein (CRP), hypercoagulation, comorbiding abnormalities of liver function, electrolyte disorder and hypoproteinemia, as Table 1 demonstrates.

The diagnosis of dermatologic toxicities was definite, graded as a maculopapular rash (G3), pruritus (G3), and bullous dermatitis (G3~4), according to the management of immunotherapy-related toxicities in the National Comprehensive Cancer Network (NCCN) Guidelines. No other diagnosis could be established except for skin infection, given the patient's refusal to perform a skin biopsy.

Following an urgent dermatology consultation, the patient was initially treated with intravenous methylprednisolone sodium succinate at 0.5mg/kg every day for the first week of hospitalization, equivalent to 40mg once daily. From the second week, it was replaced with prednisone 50mg orally and tapered by 5mg weekly. In parallel with the glucocorticoids, the patient was treated orally with TCM prescriptions for eight weeks as an integrative treatment to accelerate rash relief and alleviate itching, as shown in Table 2. The TCMs were purchased steadily from three pharmaceutical manufacturers certified under the Good Manufacturing Practice (GMP) and decocted into 400mL for oral administration twice daily. In addition, antihistamines were given regularly for three weeks, with topical halometasone and antibiotic cream as necessary.

The patient no longer developed fresh blisters or papules from the second week of hospitalization, with decreased CRP and essentially normal electrolytes and albumin. However, symptoms such as thirst, self-consciousness of dryness and heat, hyperphagia, irritability began to appear, which were considered to be aggravation of heat-toxins after glucocorticoid application. Hence, the TCM was strengthened with herbs to clear heat, detoxify toxins, and nourish Yin.

Following four weeks of integrative treatment, the patient's blisters and papules covered less than 20% of the BSA and were barely itching locally. Antihistamines and other drugs were then terminated. He received only TCM decoction and continued to reduce the dosage of glucocorticoids. By May 9th, 2023, the rash was well controlled, and the ulcers had healed without itching or pain, free of restrictions in daily life. The patient was assessed as stable disease (SD) and transferred to a specialized hospital for further anti-tumor therapies (Figure 2).

Discussion

Notably, this case demonstrates a rare clinical scenario where G3-4 cutaneous toxicity induced by PD-1 inhibitors was successfully controlled by a synergistic TCM-glucocorticoid approach, suggesting novel therapeutic combinations for severe immune-related dermatologic complications.

Typically, high-dose glucocorticoids should not be tapered before the rash relieve to G1, which would lead to a potential conflict with ICIs, already proven as a prognostic hazard for cancer patients.[18] Instead, this patient rapidly stabilized without further rashes and initiated glucocorticoid reduction upon the TCM intervention. This brought him out of the acute phase smoothly with the least glucocorticoid-induced adverse events.

Table 1 Laboratory Data

Index	Day 1 (03–06-2023)	Day 7 (03–22-2023)	Day 13 (03–28-2023)	Day 22 (04–06-2023)
EO% (%)	9	0.1	0.1	0.2
CRP (mg/L)	63.71	3.87	<0.5	<0.5
K^+ (mmol/L)	3.44	3.96	3.97	3.79
Na^+ (mmol/L)	131.3	139.6	141	139.8
ALB (g/L)	28.9	34.7	32.8	36.8
ALT (U/L)	6	63	14	15
AST (U/L)	20	81	14	17
PT (s)	13.1	11.0	10.7	9.9
D-Dimer (mg/L)	2.02	0.73	0.25	0.16
FOB	Weekly positive	Negative	Negative	Negative

Abbreviations: EO, eosinophil; CRP, c-reactive protein; K^+, potassium ion; Na^+, sodium ion; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; PT, prothrombin time; FOB, fecal occult blood.

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Table 2 TCM Prescriptions for the Patient from week 1 to week 8 of Hospitalization

Medication	Batch Number*	First Period of TCM (hospital Days 1–7) (g)	Second Period of TCM (hospital Weeks 2–8) (g)
Astragali Radix	21051001[a]	40	40
Atractylodis Macrocephalae Rhizoma	2210081	20	20
Saposhnikoviae Radix	21011616[a]	15	12
Moutan Cortex	21111116[a]	15	15
Arnebiae Radix	2205130	15	15
Rubiae Radix et Rhizoma	2209001	12	12
Ecliptae Herba	2211166	30	30
Schisandrae Chinensis Fructus	2211032	10	10
Glycyrrhizae Radix et Rhizoma	2208017	20	20
Gentianae Radix et Rhizoma	2209082	12	–
Schizonepetae Herba Carbonisata	2203026	12	–
Portulacae Herba	2211145	20	–
Poriae Cutis	2209012	15	–
Coicis Semen	2209060	30	–
Mume Fructus	2209051	10	–
Amomi Fructus	22011702[a]	6	–
Bubali Cornu	2210119	–	30
Rehmanniae Radix	22021803[a]	–	30
Paeoniae Radix Rubra	2206034	–	15
Mori Cortex	2211137	–	20
Aurantii Fructus	2208052	–	15
Sophorae Flavescentis Radix	2202013	–	12
Ophiopogonis Radix	22021702[b]	–	15

Notes: [a]TCMs were purchased from Ming Hui Heng Tong Pharmaceutical Co., Ltd. (Beijing, China). [b]The Ophiopogonis Radix was purchased from Shi Zhen Tang Ba Dong Pharmaceutical Co., Ltd. (Hubei, China). *All other TCMs were purchased from Sheng Shi Long Pharmaceutical Co., Ltd. (Beijing, China).

According to published research, receiving specialized therapy for dermatologic toxicities has been demonstrated to be an independent favorable factor for superior oncologic survival.[19] Nevertheless, the pathogenesis of irAE remains dominated by T cell over-recognition of non-self, macrophage-mediated toxicity, and activated B cell-derived antibody,[20] which logically leads to the strategy of immunosuppression, promoting glucocorticoid to a critical role on irAE.[21]

In a published case of bullous pemphigoid associated with pembrolizumab,[22] methylprednisolone at 80mg/day was used intravenously for ten days to cease the formation of new blisters, besides topical ointment, similar to our glucocorticoid-based regimen. Meanwhile, the patient took four months to taper off followed by five months continuous therapy and even developed a pulmonary fungal infection, which was suspected to be related to the prolonged use of glucocorticoids. With this, optimizing the duration of glucocorticoid use is necessary. Unfortunately, no published trial of complementary and alternative therapies has been identified for Pembrolizumab-related dermatologic toxicities. Another case explored the feasibility of using herbs targeting immunoregulation alone, such as Periostracum Cicadae, in treating Sintilimab-induced lichenoid dermatitis.[23] However, there is no more credible evidence that supports the superiority of TCM over steroids in autoimmune blistering disease, probably attributable to differences among TCM prescriptions.[24] The contest suggests that triggering the master regulators in TIME, beyond traditional syndrome differentiation, is essential.

The patient initially received a TCM prescription with Yu-Ping-Feng as one of the major constituents, which has been identified to significantly promote the infiltration of natural killer cells, and down-regulated immunosuppressive cytokines like transforming growth factor beta (TGF-β), interleukin-10 (IL-10) and indoleamine 2,3-dioxygenase in Lewis lung cancer.[25] Another vital pair, the *Arnebiae Radix, Rubiae Radix et Rhizoma*, and *Ecliptae Herba*, are chosen from the desensitizing (Tuo-Min) decoction invented by prestigious Chinese physician Prof. Zuwang Gan for allergic diseases through dispersing blood stasis, eliminating heat-toxin, and dispelling rash. The components extracted from *Arnebiae Radix* can be the anti-inflammatories via phospho-ERK and NF-κB signaling pathways and the regulator of tumor necrosis factor alpha (TNF-α).[26] *Rubiae Radix et*

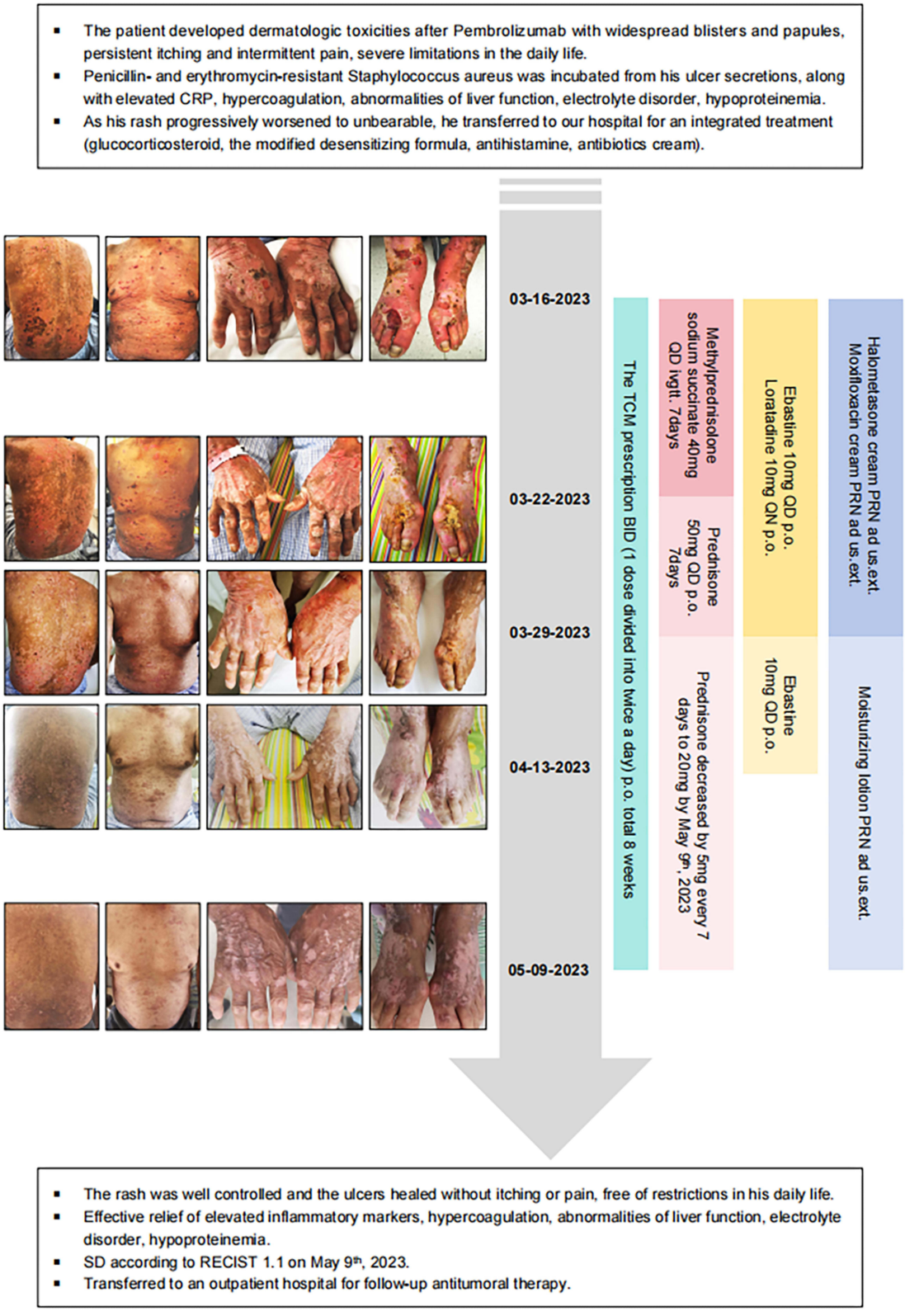

Figure 2 The timeline of this case.
Abbreviations: CRP, C-reactive protein; QD, quaque die; QN, quaque nocte; BID, bis in die; PRN, pro re nata; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

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Rhizoma and *Ecliptae Herba* have been proven to affect keratinocyte differentiation[27] as well as p53-mediated apoptosis,[28] a powerful and pan-distributed anti-oncogene. Additional herbs are used to relieve the patient's damp-heat syndrome recognized by cutaneous symptoms.

Whereas, after a week of intravenous methylprednisolone sodium succinate, the patient developed thirst, self-consciousness of dryness and heat, hyperphagia, and irritability. These symptoms were implicated in the suppressed endocrine and regulated hypothalamic kinase[29] by glucocorticoids, categorized as aggravation of heat-toxin in blood and deficiency of Yin. Thus, we removed damp-dispelling herbs to protect Yin, and replaced herbs clearing the Qi system with *Bubali Cornu* and *Sophorae Flavescentis Radix* to enhance the removal of heat-toxin. And the addition of *Mori Cortex, Aurantii Fructus*, and *Ophiopogonis Radix*, nourishing Yin without retaining the lingering pathogen, was inspired by the Gan-Lu-Yin recorded in the "Formularies of the Bureau of People's Welfare Pharmacies".

The patient's stable status and normal liver function allowed a safe switch from intravenous methylprednisolone to oral prednisone, a prodrug requiring hepatic activation. Prednisone's longer half-life (vs prednisolone) supports once-daily dosing, improving adherence and enabling smoother dose tapering with fewer hormonal fluctuations. Additionally, its lower cost and formulary availability ensured treatment accessibility without compromising efficacy.

Overall, the patient survived with more obvious alleviation, earlier glucocorticoid tapering, and fewer adverse hormonal effects, without tumor progression, on our novel integrated glucocorticoids and TCM strategy. While, to our regret, the patient rejected the further evaluation of pathological confirming diagnosis for his follow management, we therefore only clinically graded his cutaneous symptoms according to NCCN guidelines. In addition, the efficacy of this integrative treatment remains to be demonstrated by higher-grade evidence.

Conclusion

This case report indicates that integrated glucocorticoids and TCM is a favorable strategy in treating high-grade irAE dermatologic toxicity related to Pembrolizumab.

Ethics Approval and Consent to Participate

This case report was conducted in accordance with the ethical standards of the Ethics Committee of Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, and institutional approval for case publication was obtained from Beijing Hospital of Traditional Chinese Medicine, Capital Medical University. Written informed consent was obtained from the patient for the publication of anonymized clinical details and accompanying images. The patient acknowledged full understanding of the purpose of this publication and confirmed no objections to the use of relevant data for academic purposes.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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