<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>5934</td>
<td>Development of clustered regularly interspaced short palindromic repeats/CRISPR-associated technology for potential clinical applications</td>
<td>Huang YY, Zhang XY, Zhu P, Ji L</td>
</tr>
<tr>
<td>5946</td>
<td>Strategies and challenges in treatment of varicose veins and venous insufficiency</td>
<td>Gao RD, Qian SY, Wang HH, Liu YS, Ren SY</td>
</tr>
<tr>
<td>5957</td>
<td>Diabetes mellitus susceptibility with varied diseased phenotypes and its comparison with phenome interactome networks</td>
<td>Rout M, Kour B, Vuree S, Lulu SS, Medicherla KM, Suravajhala P</td>
</tr>
<tr>
<td>5965</td>
<td>Identification of potential key molecules and signaling pathways for psoriasis based on weighted gene co-expression network analysis</td>
<td>Shu X, Chen XX, Kang XD, Ran M, Wang YL, Zhao ZK, Li CX</td>
</tr>
<tr>
<td>6001</td>
<td>Effectiveness and postoperative rehabilitation of one-stage combined anterior-posterior surgery for severe thoracolumbar fractures with spinal cord injury</td>
<td>Zhang B, Wang JC, Jiang YZ, Song QF, An Y</td>
</tr>
<tr>
<td>6009</td>
<td>Prostate sclerosing adenopathy: A clinicopathological and immunohistochemical study of twelve patients</td>
<td>Feng RL, Tao YP, Tan ZY, Fu S, Wang HF</td>
</tr>
<tr>
<td>6021</td>
<td>Value of magnetic resonance diffusion combined with perfusion imaging techniques for diagnosing potentially malignant breast lesions</td>
<td>Zhang H, Zhang XY, Wang Y</td>
</tr>
<tr>
<td>6032</td>
<td>Scar-centered dilation in the treatment of large keloids</td>
<td>Wu M, Gu JY, Duan R, Wei BX, Xie F</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>6050</td>
<td>Influences of etiology and endoscopic appearance on the long-term outcomes of gastric antral vascular ectasia</td>
<td>Kwon HJ, Lee SH, Cho JH</td>
</tr>
<tr>
<td>6060</td>
<td>Evaluation of the clinical efficacy and safety of TST33 mega hemorrhoidectomy for severe prolapsed hemorrhoids</td>
<td>Tao L, Wei J, Ding XF, Ji LJ</td>
</tr>
<tr>
<td>6069</td>
<td>Sequential chemotherapy and icotinib as first-line treatment for advanced epidermal growth factor receptor-mutated non-small cell lung cancer</td>
<td>Sun SJ, Han JD, Liu W, Wu ZY, Zhao X, Yan X, Jiao SC, Fang J</td>
</tr>
<tr>
<td>6082</td>
<td>Impact of preoperative carbohydrate loading on gastric volume in patients with type 2 diabetes</td>
<td>Lin XQ, Chen YR, Chen X, Cai YP, Lin JX, Xu DM, Zheng XC</td>
</tr>
<tr>
<td>6091</td>
<td>Efficacy and safety of adalimumab in comparison to infliximab for Crohn's disease: A systematic review and meta-analysis</td>
<td>Yang HH, Huang Y, Zhou XC, Wang RN</td>
</tr>
<tr>
<td>6105</td>
<td>Successful treatment of acute relapse of chronic eosinophilic pneumonia with benralizumab and without corticosteroids: A case report</td>
<td>Izhakian S, Pertzov B, Rosengarten D, Kramer MR</td>
</tr>
<tr>
<td>6119</td>
<td>Hepatic epithelioid hemangioendothelioma after thirteen years' follow-up: A case report and review of literature</td>
<td>Mo WF, Tong YL</td>
</tr>
<tr>
<td>6128</td>
<td>Effectiveness and safety of ultrasound-guided intramuscular lauromacrogol injection combined with hysteroscopy in cervical pregnancy treatment: A case report</td>
<td>Ye JP, Gao Y, Lu LW, Ye YJ</td>
</tr>
<tr>
<td>6136</td>
<td>Carcinoma located in a right-sided sigmoid colon: A case report</td>
<td>Lyu LJ, Yao WW</td>
</tr>
</tbody>
</table>
Contents

6148 Overlapping syndrome of recurrent anti-N-methyl-D-aspartate receptor encephalitis and anti-myelin oligodendrocyte glycoprotein demyelinating diseases: A case report
Yin XJ, Zhang LF, Bao LH, Feng ZC, Chen JH, Li BX, Zhang J

6156 Liver transplantation for late-onset ornithine transcarbamylase deficiency: A case report

6163 Disseminated strongyloidiasis in a patient with rheumatoid arthritis: A case report
Zheng JH, Xue LY

6168 CYP27A1 mutation in a case of cerebrotendinous xanthomatosis: A case report
Li ZR, Zhou YL, Jin Q, Xie YY, Meng HM

6175 Postoperative multiple metastasis of clear cell sarcoma-like tumor of the gastrointestinal tract in adolescent: A case report
Huang WP, Li LM, Gao JB

6184 Toripalimab combined with targeted therapy and chemotherapy achieves pathologic complete response in gastric carcinoma: A case report

6192 Presentation of Boerhaave’s syndrome as an upper-esophageal perforation associated with a right-sided pleural effusion: A case report
Tan N, Luo YH, Li GC, Chen YL, Tan W, Xiang YH, Ge L, Yao D, Zhang MH

6198 Camrelizumab-induced anaphylactic shock in an esophageal squamous cell carcinoma patient: A case report and review of literature

6205 Nontraumatic convexal subarachnoid hemorrhage: A case report
Chen HL, Li B, Chen C, Fan XX, Ma WB

6211 Growth hormone ameliorates hepatopulmonary syndrome and nonalcoholic steatohepatitis secondary to hypopituitarism in a child: A case report
Zhang XY, Yuan K, Fang YL, Wang CL

6218 Vancomycin dosing in an obese patient with acute renal failure: A case report and review of literature
Xu KY, Li D, Hu ZJ, Zhao CC, Bai J, Du WL

6227 Insulinoma after sleeve gastrectomy: A case report
Lobaton-Ginsberg M, Sotelo-González P, Ramirez-Renteria C, Juárez-Aguilar FG, Ferreira-Hermosillo A

6234 Primary intestinal lymphangiectasia presenting as limb convulsions: A case report
Cao Y, Feng XH, Ni HX

6241 Esophagogastric junctional neuroendocrine tumor with adenocarcinoma: A case report
Kong ZZ, Zhang L
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>6247</td>
<td>Foreign body granuloma in the tongue differentiated from tongue cancer</td>
<td>Jiang ZH, Xu R, Xia L</td>
</tr>
<tr>
<td>6261</td>
<td>Management of type IIIb dens invaginatus using a combination of root canal treatment, intentional replantation, and surgical therapy: A case report</td>
<td>Zhang J, Li N, Li WL, Zheng XY, Li S</td>
</tr>
<tr>
<td>6277</td>
<td><em>De novo</em> brain arteriovenous malformation formation and development: A case report</td>
<td>Huang H, Wang X, Guo AN, Li W, Duan RH, Fang JH, Yin B, Li DD</td>
</tr>
<tr>
<td>6283</td>
<td>Coinfection of <em>Streptococcus suis</em> and <em>Nocardia asiatica</em> in the human central nervous system: A case report</td>
<td>Chen YI, Xue XH</td>
</tr>
<tr>
<td>6289</td>
<td>Dilated left ventricle with multiple outpouchings — a severe congenital ventricular diverticulum or left-dominant arrhythmogenic cardiomyopathy: A case report</td>
<td>Zhang X, Ye RY, Chen XP</td>
</tr>
<tr>
<td>6307</td>
<td>Thyroid follicular renal cell carcinoma excluding thyroid metastases: A case report</td>
<td>Wu SC, Li XY, Liao BJ, Xie K, Chen WM</td>
</tr>
<tr>
<td>6314</td>
<td>Appendiceal bleeding: A case report</td>
<td>Zhou SY, Guo MD, Ye XH</td>
</tr>
<tr>
<td>6319</td>
<td>Spontaneous healing after conservative treatment of isolated grade IV pancreatic duct disruption caused by trauma: A case report</td>
<td>Mei MZ, Ren YF, Mou YP, Wang YY, Jin WW, Lu C, Zhu QC</td>
</tr>
<tr>
<td>6325</td>
<td>Pneumonia and seizures due to hypereosinophilic syndrome—organ damage and eosinophilia without synchronisation: A case report</td>
<td>Ishida T, Murayama T, Kobayashi S</td>
</tr>
</tbody>
</table>

**LETTER TO THE EDITOR**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>6338</td>
<td>Stem cells as an option for the treatment of COVID-19</td>
<td>Cuevas-González MV, Cuevas-González JC</td>
</tr>
</tbody>
</table>
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Pembrolizumab-induced Stevens-Johnson syndrome in advanced squamous cell carcinoma of the lung: A case report and review of literature

Jing-Yi Wu, Kai Kang, Jing Yi, Bin Yang

Abstract

BACKGROUND
For advanced lung squamous cell carcinoma, immune checkpoint inhibitors (ICIs) have been regarded as one of the optimal therapies. While immune-related adverse events (irAEs) are common in ICI treatment, cutaneous toxicities are among the most common irAEs. Most immune-related skin toxicity grades are low, and the prognosis is good. However, Stevens-Johnson syndrome (SJS) is a rare but extremely severe cutaneous adverse drug reaction with high mortality.

CASE SUMMARY
We report a rare case of SJS induced by pembrolizumab. The case involved a 68-year-old female who was diagnosed with advanced squamous cell carcinoma of the lung. SJS appeared after one cycle of immunotherapy combined with chemotherapy. After treatment with prednisone hormone symptoms, anti-infection, gamma globulin, and antipruritic agents, the skin toxicity of the patients gradually decreased and eventually disappeared. Although the antitumor treatment was stopped due to serious adverse reactions, the tumor of the patient remained stable for nearly half a year after one cycle of immune therapy combined with chemotherapy, which also corroborates the delayed effect of immunotherapy.

CONCLUSION
We believe our report can provide some references for the treatment of SJS and the treatment of immune-related adverse reactions.
Key Words: Pembrolizumab; Stevens-Johnson syndrome; Advanced squamous cell carcinoma; Lung; Immune-related adverse events; Case report

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Core Tip: Stevens-Johnson syndrome (SJS) is a rare but extremely severe cutaneous adverse drug reaction with high mortality. The case involved a 68-year-old female who was diagnosed with advanced squamous cell carcinoma of the lung. SJS syndrome appeared after one cycle of immunotherapy. After the optimal supportive treatment, skin toxicity disappeared.

INTRODUCTION
Pembrolizumab is an anti-PD-1 (programmed death 1) humanized IgG4 monoclonal antibody that blocks the PD-1 receptor to enable T cell killing. Pembrolizumab, combined with chemotherapy, has shown improved efficacy in patients with advanced squamous cell carcinoma of the lung[1], with drug-related adverse events reported in 64% of patients[2]. However, adverse events of grade 3 or higher were reported in less than 10% of patients and included cutaneous side-effect cases.

Stevens-Johnson syndrome (SJS) is a severe type of pleomorphic erythema and a rare adverse mucocutaneous reaction with a mortality rate of up to 35%[3]. While SJS is characterized by maculopapular rash – pruritus – and is often related to adverse drug reactions[4,5], the mechanism of SJS has not been determined. It has been reported that at least 200 kinds of drug reactions are related to SJS. However, cases in which anti-PD-1/anti-PD-L1 drugs contribute to SJS are rare[3]. There have been several reports of anti-PD-1/anti-PD-L1 therapy inducing SJS[6-14,15]. Here, we present our report of a rare case of pembrolizumab-associated SJS in a female patient with advanced squamous cell carcinoma of the lung.

CASE PRESENTATION
Chief complaints
The patient was a 68-year-old female without a history of smoking. On October 1st, 2020, she was admitted due to repeated cough and breathlessness for 1 mo.

History of present illness
Systemic examinations, including chest computed tomography (CT), whole abdominal CT, brain magnetic resonance imaging (MRI), bone scintigraphy, and blood tests, were performed. The test results showed that the levels of tumor markers were clearly elevated, and CT indicated a lung mass in the right lobe, several bilateral nodules, multiple mediastinal lymph nodes, and a solitary liver metastasis. Squamous cell carcinoma of the lung was diagnosed through CT-guided percutaneous needle lung biopsy, and polymerase chain reaction (PCR) revealed no epidermal growth factor receptor, anaplastic lymphoma kinase, or receptor tyrosine kinase mutations. According to the American Joint Commission on Cancer 8th edition staging system, she was clinically diagnosed with stage IVA lung squamous cell carcinoma (cT4N2M1b). According to the 2020 National Comprehensive Cancer Network guidelines, the combination of immunotherapy and chemotherapy is the best optional treatment for patients with advanced lung squamous cell carcinoma. On October 14, 2020, the patient was treated with one cycle of paclitaxel 270 mg d1 + cisplatin 120 mg d1 chemotherapy combined with pembrolizumab therapy. On November 4, 2021, which was nearly three weeks after one cycle of chemotherapy, the patient started with low fever, sore throat, and severe fatigue. Then, the patient was considered to be related to cold exposure. Penicillin treatment was used in the hospital nearby, but the patient's symptoms did not improve, which lasted for almost 5 d. On November 9th, small papules and typical erythema, accompanied by severe itchiness and general discomfort, gradually appeared on the patient's skin and were mainly distributed in the anterior chest and face. Considering the severity of the patient's
symptoms, the patient visited our hospital on November 12th. The patient’s temperature was normal. The pain in her throat persisted. The physical examination of the patient showed that multiple erythematous papules could be detected on the patient’s head, neck, chest, and back (covering 30% of the total body skin) (Figure 1), most of which fused to form blisters. The patient reported that these papules felt mild itchiness but painful. Eyelid edema was obvious. There were some ulcers around the lip. The patient’s oral ulcers were too painful to allow her to eat anything.

**History of past illness**
There was no remarkable past medical history with no alcohol consumption or history of smoking.

**Personal and family history**
Family and personal history were unremarkable. She had no significant medical history or drug allergy.

**Physical examination**
A poor general condition, SCORTEN (severity-of-illness score for TEN) score of 4 points. Nikolsky’s sign was positive. Koebner phenomenon was negative. Erythematous papules could be detected on the patient’s head, neck, chest, and back (covering 30% of the total body skin) with mild itchy but painful symptoms. Eyelid edema was obvious. There were some ulcers around the lip. Her oral ulcers were too painful to allow her to eat anything. No other apparently positive signs were found.

**Laboratory examinations**
She was admitted to our hospital, and the relevant blood tests after admission are shown in Table 1 below.

**Imaging examinations**
Chest and abdominal CT scans showed that the primary lung lesions and liver metastases were significantly reduced, and the overall response evaluation was PR according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors).

**FINAL DIAGNOSIS**
We arranged an urgent consultation with a dermatologist. According to the skin and mucous membrane performance of the patient during these days, the rapid development of the disease, and history of PD-1 inhibitor use, pembrolizumab-induced SJS was diagnosed.

**TREATMENT**
Therefore, we immediately administered moderate- to high-potency topical steroids to treat the affected areas, oral antihistamines for pruritus and oral prednisone at 40 mg/d. After three days of treatment, the dermatologic toxicities were clearly aggravated. On November 18 (Figure 2), the rash began to spread to almost the entire body (covering more than 45% of the total body skin). The blisters were formed superficially in the epidermis with skin ulceration, and most of them had blood and fluid oozing. Part of the epidermis was peeled off from the surface of the body, exposing a moist, painful, flushed erosive surface. The oral ulcers continued to be aggravated. Both the itchiness and pain worsened, and the patient became severe (G3-4). At this point, we suspended immunotherapy, administered high potency topical steroids to the affected areas and prophylactically used antibiotics; additionally, we increased the prednisone dose to 100 mg. After three days of treatment, the cutaneous toxicities continued to worsen (Figure 3).

**OUTCOME AND FOLLOW-UP**
By referring to the opinions from the consultation, intravenous methylprednisolone 120 mg/d (2 mg/kg/d), gamma globulin 20 g/d, topical gentamicin, and diluted potassium permanganate were administered. Sepprayi 25 mg (recombinant human type II tumor necrosis factor receptor-antibody fusion protein, rhTNFR:Fc) was injected subcutaneously twice a week, and oral antihistamine was administered for pruritus. After a week of treatment, the dermatologic toxicities were gradually alleviated (Figure 4). Then, oral prednisone was gradually reduced, and topical drug administration continued. The treatment lasted for 3 mo, and the skin toxicity eventually disappeared (Figure 5). In terms of lung carcinoma, the pulmonary nodule was smaller than the baseline and remained stable during the 6-mo evaluation. In May 2021, the latest re-examination showed that although the patient did
### Table 1 Some blood test of the patient

<table>
<thead>
<tr>
<th>Time</th>
<th>November 18, 2021</th>
<th>November 26, 2021</th>
<th>December 1, 2021</th>
<th>December 7, 2020</th>
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<tbody>
<tr>
<td>White blood cell</td>
<td>10.3×10⁸/L (3.5-9.5)</td>
<td>10.01×10⁸/L (3.5-9.5)</td>
<td>9.28×10⁸/L (3.5-9.5)</td>
<td>10.76×10⁸/L (3.5-9.5)</td>
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<tr>
<td>Red blood cell</td>
<td>2.68×10¹²/L (3.8-5.1)</td>
<td>3.01×10¹²/L (3.8-5.1)</td>
<td>2.86×10¹²/L (3.8-5.1)</td>
<td>2.63×10¹²/L (3.8-5.1)</td>
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<tr>
<td>Hemoglobin</td>
<td>78 g/L (115-150)</td>
<td>98 g/L (115-150)</td>
<td>97.9 g/L (115-150)</td>
<td>89.3 g/L (115-150)</td>
</tr>
<tr>
<td>Thrombocyte</td>
<td>115×10⁹/L (125-350)</td>
<td>124×10⁹/L (125-350)</td>
<td>135×10⁹/L (125-350)</td>
<td>133×10⁹/L (125-350)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>22.07 mg/L (0-10)</td>
<td>60.5 mg/L (0-10)</td>
<td>44 mm/h (0-22)</td>
<td>51 mm/h (0-22)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>0.05 ng/mL (&lt; 0.05)</td>
<td>0.05 ng/mL (&lt; 0.05)</td>
<td>0.09 ng/mL (&lt; 0.05)</td>
<td>0.09 ng/mL (&lt; 0.05)</td>
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<tr>
<td>D-dimer</td>
<td>0.83 ng/mL (&lt; 0.5 mg/L)</td>
<td>646 ng/mL (&lt; 0.5 mg/L)</td>
<td>22.2 g/L (7.0-12.6)</td>
<td></td>
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<tr>
<td>Immunoglobulin G (IgG)</td>
<td>22.2 g/L (7.0-12.6)</td>
<td>22.2 g/L (7.0-12.6)</td>
<td>22.2 g/L (7.0-12.6)</td>
<td>22.2 g/L (7.0-12.6)</td>
</tr>
<tr>
<td>ANA reaction</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>ANA drop degree</td>
<td>0.486</td>
<td>0.486</td>
<td>0.486</td>
<td>0.486</td>
</tr>
<tr>
<td>Anti-SSA/Ro antibody</td>
<td>Strongly positive (+++)</td>
<td>Strongly positive (+++)</td>
<td>Strongly positive (+++)</td>
<td>Strongly positive (+++)</td>
</tr>
<tr>
<td>Anti-SSB</td>
<td>Positive (++)</td>
<td>Positive (++)</td>
<td>Positive (++)</td>
<td>Positive (++)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>39.26 pg/mL (0-7)</td>
<td>39.26 pg/mL (0-7)</td>
<td>39.26 pg/mL (0-7)</td>
<td>39.26 pg/mL (0-7)</td>
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</table>

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Figure 1 Multiple erythematous papules can be detected on the patient’s head, neck, chest and back (covering 30% of the total body skin).

not receive any antitumor treatment, the lesion remained stable.

**DISCUSSION**

Since the 21st century, the introduction of immunotherapy treatments has dramatically revolutionized the treatment paradigm of non-small-cell lung cancer (NSCLC)[16]. However, immune checkpoint inhibition usually leads to systemic adverse reactions, which are immune-related adverse events, mainly encompassing rash, colitis, pneumonitis, hepatitis, and thyroiditis[17]. Dermatologic toxicities seem to be the most frequently reported adverse events. SJS is a rare and severe dermatologic toxicity with high mortality[4]. The first SJS case induced by pembrolizumab in NSCLC was reported in a Japanese case[14]. Our case report is the first Chinese case of pembrolizumab-associated SJS in NSCLC.

At present, the exact mechanism of SJS remains undefined. The currently recognized theory is the T cell-mediated type IV delayed hypersensitivity reaction[18,19]. The drug triggering SJS binds the T cell receptor and MHC class I, and as a result, it leads to the massive replication of cytotoxic T cells, which
directly kill keratinocytes, and the release of granulysin, which destroys cells in the skin and the mucous membrane\cite{20}. Yun-Shiu’s research showed that the blockade of PD-1/PD-L1 may contribute to the imbalance of the immune system, manifesting the enhancement of the T cell response and increasing the incidence of hypersensitivity\cite{21}. During the treatment of SJS induced by ipilimumab and nivolumab in a melanoma patient\cite{22}, an increase in CD8+ T cells in the dermal epidermal junction and an increase in
Figure 4 After a week of treatment, the dermatologic toxicities were gradually alleviated. A: The itchiness of the patient was significantly relieved, large blisters and ulcers basically disappeared; B: The dermis began to recover gradually.

Figure 5 The patient recovered very well.

PD-L1 expression in keratinocytes were noted. Unfortunately, the biopsy analysis of our case has not been finished, and therefore, this viewpoint cannot be further confirmed. Overall, the mechanism of SJS caused by immunosuppressive drugs requires further research.

Cutaneous toxicities of immune checkpoint inhibitors might result in a longer PFS (progression-free survival) and a higher OS (overall survival) rate[23]. Bairavi and his colleagues demonstrated that NSCLC patients with one irAE and multisystem irAEs incrementally improved OS and PFS. Longer immune checkpoint inhibitor durations were an independent risk factor for the development of irAEs. In our case, it was rare that such severe AEs occurred after just one cycle of immunotherapy[24]. Susana also indicated that the median PFS was 9.49 mo in the group with irAEs vs 1.99 mo in the group without irAEs ($P < 0.0001$) in NSCLC treated with nivolumab[25]. In our case, the condition of the patient was stable for up to 6 mo just after one cycle of the treatment. Thus, we speculate that skin toxicities and delayed immunological effects both contributed to such a long progression-free survival time.

There is no standard treatment regimen for SJS[26], and multidisciplinary care, best supportive care, and corticosteroids are currently the most important components of its therapy[20]. By applying high-dose corticosteroids early, we can rapidly arrest SJS, while the optimal cutoff time of corticosteroids remains controversial because of its adverse drug reaction[27]. From the author’s perspective, the appropriate duration of high-dose corticosteroids is within 4 wk. The combination of IVIG and steroids seems to bring better outcomes to patients with SJS[28].

In addition to corticosteroids and IVIG, drugs that suppress the immune response or inflammatory factors are also being tried in the treatment of SJS. Over the last several years, several retrospective trials have advocated the benefits of cyclosporine in the treatment of SJS/TEN[29,30]. Cyclosporine inhibits
the activation of CD4+ and CD8+ T cells in the early phase, subsequently inhibiting the secretion of granulysin, granzyme, and perforin[31]. Despite a lack of randomized control trials, cyclosporine has proven to have a mortality benefit in the treatment of SJS/TEN without a low risk of side effects. In our case, we did not use cyclosporine due to the lack of experience in the early phase of treatment for SJS. In the late phase, we used recombinant human tumor necrosis factor receptor type II-Fc fusion protein antibody as recommended by the dermatologist. The reason we used Sepprayi is that it can reduce the level of inflammatory factors, such as tumor necrosis factor-α (TNF-α), inhibiting the occurrence of hypersensitivity[32]. In our case, Sepprayi had a clear effect on the improvement of the patient's inflammatory response. However, more clinical practice and data support are needed due to limited trials.

CONCLUSION

Immunotherapy, as a new treatment in the 2010s, has a definite effect on the treatment of advanced lung cancer. However, there remain many difficulties to be overcome in the treatment of serious adverse reactions related to immunotherapy. The combination of high-dose corticosteroid shock therapy, IVIG, cyclosporine, and best supportive care might reduce mortality in the treatment of SJS. The incidence of serious immune-related skin toxicity, such as SJS, is low, but the lethality is still very high. However, there is still a long way to go for immune-related adverse events, such as predictors for adverse events and ways to prevent them in advance. In future studies, we might focus more on the prediction, prevention, and treatment of irAEs, although immunotherapy is in full swing.

FOOTNOTES

Author contributions: Wu JY and Kang K designed the study and performed the experiments; Yi J, Yang B, and Wu JY performed the experiments, analyzed the data, and wrote the manuscript; Wu JY and Kang K contributed to this article equally.

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