Pembrolizumab therapy in a patient with NSCLC and bullous pemphigoid: A case report

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Abstract. Immune checkpoint inhibitor (ICI) therapy, which targets programmed cell death protein 1, has demonstrated enhanced survival outcomes in numerous patients with cancer. Historically, individuals with autoimmune diseases have been excluded from clinical trials involving cancer immunotherapies due to concerns about the potential worsening of their underlying autoimmune conditions. In the present case report, a patient with non-small cell lung cancer and bullous pemphigoid (BP) who underwent treatment with the ICI pembrolizumab is described. In this specific clinical case, no severe exacerbation of the underlying autoimmune disease was observed. Contrarily, the patient not only tolerated pembrolizumab well but also experienced amelioration of the BP lesions after the treatment. This case challenges the conventional exclusion criteria for ICI therapy in patients with autoimmune diseases, suggesting the potential safety and efficacy of such treatments in this specific population. However, further investigations and larger-scale studies are warranted to validate these findings and provide a more comprehensive understanding of the implications of ICI therapy in patients with autoimmune comorbidities.

Introduction

Immune checkpoint inhibitor (ICI) therapy directed at programmed cell death protein 1 (PD-1) has been shown to improve survival outcomes in patients diagnosed with non-small cell lung cancer (NSCLC) (1). Anti-PD-1 antibodies, including pembrolizumab and nivolumab, are considered to exert their anticancer effects by blocking the interaction of PD-1 with programmed death-ligand 1 (PD-L1), as this interaction has an inhibitory effect on T-cell activity. However, the function of PD-L1 as a physiological regulator of the activation of CD8 T cells also prevents the development of chronic autoimmune inflammation (2). As a consequence, immune-related adverse events (irAEs) are the predominant toxicity associated with ICI therapy (3). IrAEs can impact any organ and result from the effects of immune dysregulation on normal tissues. Individuals with pre-existing autoimmune diseases are frequently excluded from clinical trials involving ICIs (4,5) due to concerns about the potential exacerbation of underlying autoimmune diseases. This limits the treatment options for these patients. Bullous pemphigoid (BP) is an autoimmune skin blistering disease characterized by the deposition of autoantibodies in the epithelial basement membrane zone (BMZ). Predominantly affecting older adults, the condition typically manifests with generalized pruritic urticarial plaques and subepithelial tension blisters (6). A recent case report has demonstrated the recurrence of BP in a patient undergoing treatment for lung cancer with pembrolizumab (7). Although retrospective studies have explored the safety of using ICIs in patients with autoimmune diseases (8), the evaluation of these drugs in various clinically relevant scenarios has been limited. The safe delivery of immunotherapy to this distinctive population without worsening their autoimmune condition presents a substantial clinical challenge as well as an unmet medical need.

The present study reports a case involving a patient diagnosed with NSCLC complicated by BP, who underwent treatment with pembrolizumab. Throughout the treatment course, the potential exacerbation of known autoimmune diseases was monitored and the antitumor effect was evaluated.

Case report

In November 2020, a 52-year-old man consulted with a dermatologist at the Affiliated Hospital of Guangdong Medical University (Zhanjiang, China) due to the presence of multiple blisters on his back, which were characterized by thick walls and a hemispheric morphology (Fig. 1A). The histopathological examination of the skin biopsy reported the presence of subepidermal blisters,

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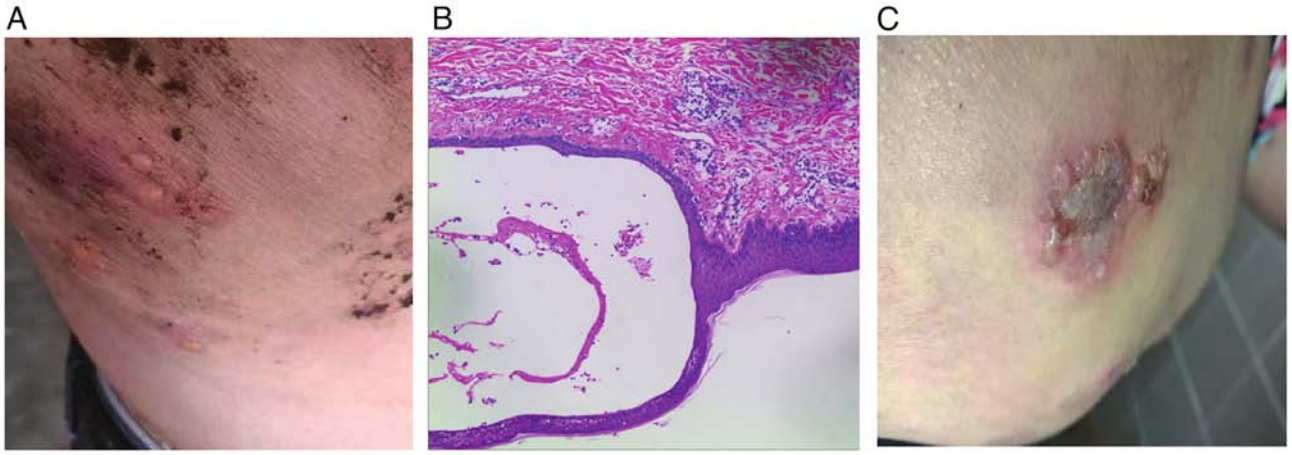

Figure 1. Dermal findings of the patient. (A) Multiple skin blisters were evident in November 2020. (B) Histopathological microphotograph of skin biopsy tissue from the bullous lesion shows subepidermal blisters with inflammatory cell infiltration, without prominent eosinophilic granulocytes (H&E stain; magnification, x40). (C) Following 3 years of treatment with prednisone, the skin blisters had not healed.

visible on HE staining, accompanied by inflammatory cell infiltration at the base of the blisters and the absence of significant eosinophils (Fig. 1B). Immunofluorescence demonstrated the presence of linear deposits of IgG, C3 and IgA within the basement membrane, which is consistent with the diagnosis of BP (data not shown). The patient initially received treatment with oral prednisone at a dose of 10 mg once daily. After 3 years of treatment, the skin symptoms improved but were not completely cured (Fig. 1C). Due to the prolonged duration of treatment, the patient neglected to monitor the progression of the disease and discontinued treatment in May 2023.

The history of NSCLC began in March 2023, when the patient experienced pain in the right chest and back. A subsequent positron emission tomography and computed tomography (PET-CT) scan revealed a maximum standardized uptake value (SUV) of 17.58, indicating a high likelihood of lung cancer. The scan also revealed multiple lymph node metastases in the bilateral clavicle area, the inner or underside surfaces of the right pectoralis major and minor muscles, as well as in the right hilum and mediastinum (Fig. 2A and C). Pathological examination following biopsy of the mass in the upper right lung indicated infiltrating adenocarcinoma, a type of NSCLC, with PD-L1 expression at 3% (Fig. S1). No genetic mutations were detected (Fig. S2).

In July 2023, the patient underwent further treatment at the Affiliated Hospital of Guangdong Medical University. CT re-examination revealed the presence of an irregular round soft tissue mass in the upper lobe of the right lung, measuring ~58x59x52 mm (Fig. 2E). Considering the previous examination results, the patient was diagnosed with cT3N3M0 stage IIIC according to the Cancer Staging Manual of the American Joint Committee on Cancer, 8th version (9). Following evaluation by a multidisciplinary team (MDT) and a comprehensive assessment of the risks and benefits associated with treatment, a combined treatment approach of pembrolizumab (200 mg every 3 weeks) and chemotherapy (pemetrexed 940 mg every 3 weeks + carboplatin 500 mg every 3 weeks) was initiated. A CT scan conducted in August 2023 indicated a noticeable reduction in tumor size (Fig. 2F). Following the completion of four cycles of combined therapy, CT (Fig. 2G) and PET-CT (Fig. 2B and D) scans were performed for re-examination. The PET-CT scan revealed a maximum SUV of 3.0, indicating a significant reduction in the size of the lung cancer lesions in the upper lobe of the right lung compared with that at the previous scan. Furthermore, the multiple lymph node metastases in the bilateral supraclavicular fossa, mediastinum and right hilar area were markedly reduced in number and smaller than before. The tumor response was evaluated as a partial response according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1 (10). The patient exhibited no adverse reactions during the treatment, and the BP showed no signs of exacerbation; instead improvements in this skin condition were observed (Fig. 3A). After four treatment cycles, the superficial BP lesions of the patient had resolved (Fig. 3B). Following immunotherapy combined with chemotherapy, the patient was diagnosed with ypT2aN0M0 stage IB. At this time, the combination therapy was completed, with no evidence of disease progression and no occurrence of any other adverse reactions. Consequently, the immunomodulatory maintenance therapy was continued. The patient's cancer indicators are now normal, with no significant side effects, and he is currently undergoing maintenance therapy with pablizumab monotherapy (200 mg every three weeks), with pre-treatment blood sampling for cancer markers and follow-up chest CT scans conducted every three months.

Discussion

In the present case, effectively managing lung cancer while not exacerbating the autoimmune disease was of the utmost importance. Symptoms stemming from tumor-secreted hormones, peptides, cytokines or immune cross-reactions between malignant and normal tissues in various organ systems are collectively referred to as paraneoplastic syndromes (11). According to a meta-analysis published in 2018, the incidence of malignant tumors in patients with BP is 11% (12). The occurrence of BP is also associated with lung cancer, mantle cell lymphoma and cutaneous squamous cell carcinoma as part of a paraneoplastic syndrome (13-15). In response to this phenomenon, various pathogenic mechanisms have been proposed. One suggestion is that, in instances where malignancy precedes BP, antibodies directed

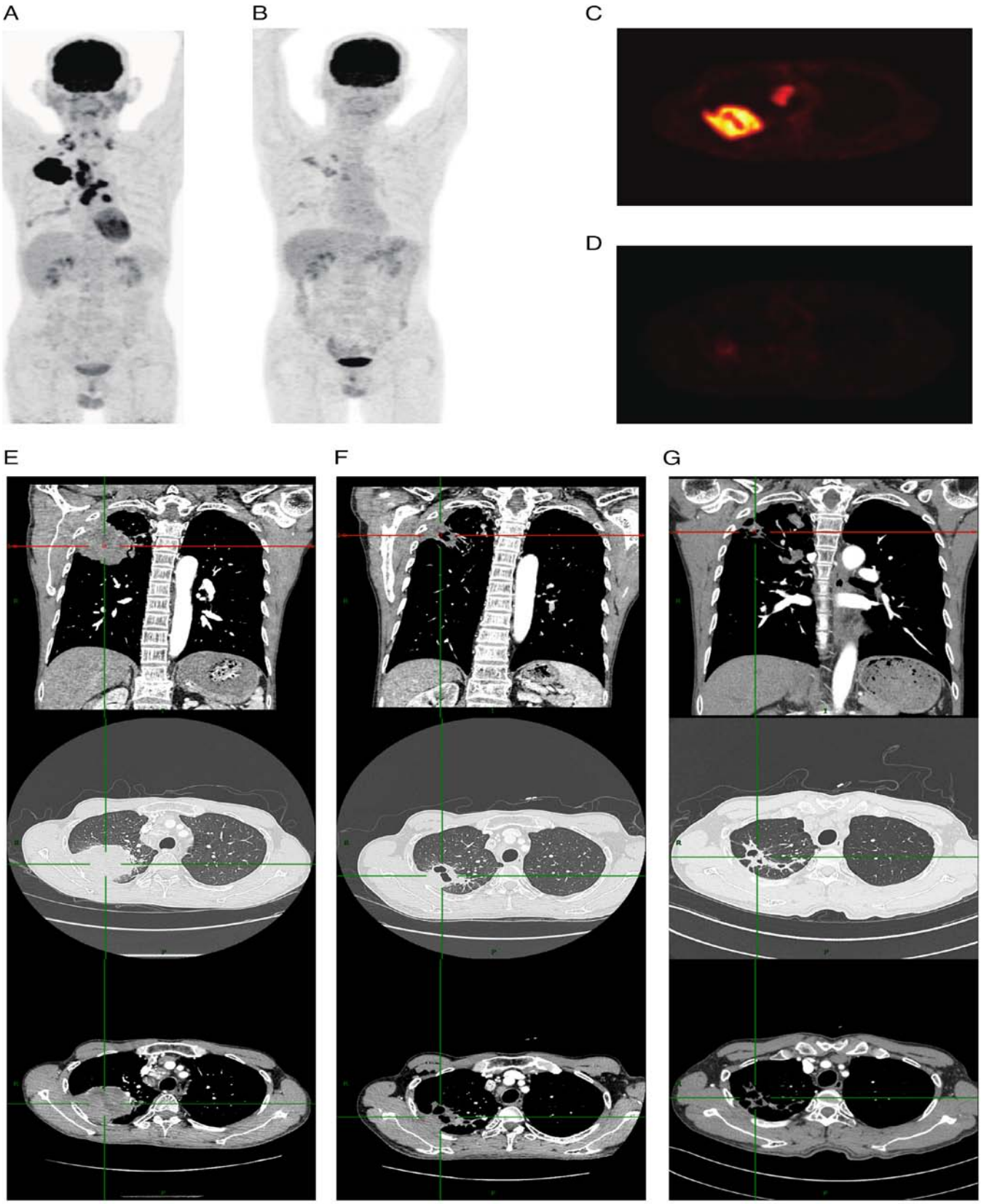

Figure 2. PET-CT and CT images of the patient at different time points. PET-CT images of the body (A) at the time of diagnosis of lung cancer and (B) after comprehensive treatment. PET-CT images of the lung (C) at the time of diagnosis and (D) after comprehensive treatment. Enhanced CT images at different angles and window levels (E) before treatment, (F) after two cycles of treatment and (G) after four cycles of treatment. Each set of images comprises three distinct panels: a upper panel, a middle panel, and a lower panel. The top panel displays coronal images of the CT mediastinal window, while the middle and bottom panels present axial images of the same slice in the lung window and mediastinal window, respectively. The images in Group E illustrate the presence of a large tumor prior to treatment, which has resulted in compression of the surrounding tissues. The images in Group F demonstrate a notable reduction in tumor volume following two cycles of treatment, accompanied by partial recovery of the lung parenchyma. The images in Group G exhibit further tumor shrinkage after four cycles of treatment, with enhanced recovery of the surrounding lung tissue and structure. PET, positron emission tomography; CT, computed tomography.

Table I. Curth's postulates for the diagnosis of cutaneous paraneoplastic syndromes.

No.	Criterion
1	Neoplasia and cutaneous condition began concurrently
2	Development followed a parallel course[a]
3	Cutaneous condition is not associated with a genetic syndrome
4	A specific type of neoplasia occurs with a characteristic cutaneous condition
5	The cutaneous condition is rare in the general population
6	High frequency of association between both conditions

[a]Treatment of the neoplasia results in regression of the skin lesion; recurrence of the neoplasia implies recurrence of the skin lesion.

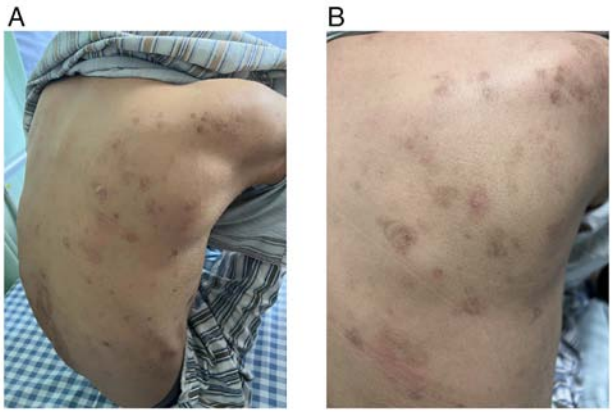

Figure 3. Amelioration of pemphigus symptoms after treatment with pembrolizumab and chemotherapy. Skin surface blisters (A) exhibited improvement in after two cycles of treatment and (B) disappeared after four cycles of treatment.

against tumor-specific antigens may cross-react with basement membrane antigens, such as BP antigens, ultimately resulting in skin blistering (16). Such an antigen may be laminin-332, a protein crucial for keratinocyte-basal cell membrane adhesion that is also produced by various solid malignancies, including breast, pancreatic, colon and lung cancer. It has also been postulated that the tumor produces anti-BMZ cross-reactive antigens or other molecules that disrupt the basement membrane, and that this disruption leads to the production of anti-BMZ antibodies (17). As of yet, no specific histopathological factors have been identified that are able to differentiate tumor-associated pemphigoid from conventional pemphigoid. Due to the concurrent discovery of BP and NSCLC in the present patient, guided by Curth's postulates (Table I) and recent studies (11-17), it was proposed that the pemphigoid may have been induced by NSCLC. Consequently, the effective treatment of the primary tumor was crucial for controlling the associated skin disease.

Recent research findings have indicated that neoadjuvant nivolumab in combination with chemotherapy significantly extends event-free survival compared with chemotherapy alone in patients with resectable NSCLC, with a higher proportion of patients achieving a pathological complete response (18). Although PD-1/PD-L1 inhibitors may induce autoimmune diseases, their efficacy in patients with pre-existing autoimmune diseases is generally comparable with that in other patients, and most irAEs are mild and manageable (19). A meta-analysis demonstrated that the addition of chemotherapy to ICIs improves their treatment efficacy in the first-line treatment of advanced NSCLC. Specifically, the combination of chemotherapy with pembrolizumab or atezolizumab exhibits consistently higher efficacy than chemotherapy alone, any other ICI-based combination or monotherapy, particularly in patients with non-squamous histology (20). In addition, in another study, pembrolizumab plus chemotherapy exhibited the optimum overall survival in patients with PD-L1 expression ≥1% In addition, pembrolizumab was associated with fewer grade ≥3 adverse events compared with other immunotherapies combined with chemotherapy (21). In the present case, following approval in the MDT meeting, a regimen involving a combination of pembrolizumab and chemotherapy was devised. The survival and response rates of cisplatin plus paclitaxel are comparable with those of carboplatin plus paclitaxel. However, as carboplatin plus paclitaxel has been shown to be associated with lower toxicity (22), carboplatin was selected for use in the present case. Due to its good efficacy and tolerability, pemetrexed remains a key agent in the treatment of patients with advanced non-squamous NSCLC (23), and pemetrexed was therefore chosen as the chemotherapy regimen for the present case. Following four cycles of treatment, the patient experienced a marked reduction in lung tumors, and the skin lesions completely disappeared. To date, the treatment has not yet concluded. Given that irAEs frequently manifest during the maintenance phase, it is imperative that the condition of the patient is monitored during the follow-up treatment period.

In conclusion, in the present case, the use of pembrolizumab combined with chemotherapy successfully reduced the size of the tumor, and the BP symptoms gradually improved. A potential paraneoplastic syndrome was suspected. However, to the best of our knowledge, no studies have examined the combination of immunosuppressive agents with chemotherapy for the treatment of autoimmune diseases. This may be due to the mechanism of action of chemotherapy not being strongly associated with the pathogenesis of autoimmune diseases. Furthermore, recent case reports have suggested that pemphigoid may recur after pembrolizumab treatment (7). Therefore, the treatment plan used in the current study holds certain importance as a clinical reference; however, its safety requires verification through use in more cases. Further exploration of the mechanism by which pemphigoid and malignant tumors are associated is also necessary. In addition, the relationship between steroid and ICI therapies is complex. It has been proposed that the use of baseline corticosteroids at

a dosage of ≥10 mg prednisone equivalent is associated with a poorer outcome in patients with NSCLC who are treated with PD-1/PD-L1 inhibitors (24). Consequently, it is suggested that this combination therapy should be used with caution and its feasibility should be further explored in future studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AL and FL were responsible for conceptualization. ZM, YP, BD and ZH were responsible for the collection and collation of clinical data and background information. AL and FL wrote the original draft of the manuscript. ZL and JC contributed to the data acquisition and analysis, and reviewed it critically for important intellectual content. AL and FL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the anonymized data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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