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CASE REPORT

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Cytokine release syndrome and successful response to pembrolizumab therapy in a patient with *EGFR*-mutated non-small-cell lung cancer: A case report

Meng Zhang | **Yuan Cheng** | **Yan Hu** | **Ligong Nie**

Department of Respiratory and Critical Care Medicine of Peking University First Hospital, Beijing, China

Correspondence
Yuan Cheng, Department of Respiratory and Critical Care Medicine of Peking University First Hospital, No. 8 Xi Shi Ku Street, Xi Cheng District, Beijing 100034, China
Email: softsnake@bjmu.edu.cn

Abstract

A therapeutic option for advanced non-small-cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) resistance is a clinical challenge. The clinical outcomes of pembrolizumab in those patients is inconclusive. Cytokine release syndrome (CRS) is a rarely reported immune-related adverse event in the field of immune checkpoint inhibitors therapy, raising challenges given the paucity of data with such presentations. We present the unique case of a 67-year-old female with advanced EGFR-mutated NSCLC who successfully responded to pembrolizumab after EGFR-TKI resistance. However, the patient developed CRS after pembrolizumab initiation and presented with fever, rash, hypotension, hypoxemia, tachycardia, and multiple organ dysfunction. Blood tests showed elevated levels of peripheral CD8+ T cells, C-reactive protein, and tumor necrosis factor-α. The symptoms rapidly improved after corticosteroid initiation. Based on the present case, we propose that pembrolizumab might be a potential salvage therapy for patients with advanced *EGFR*-mutated NSCLC after EGFR-TKI resistance; CRS would be a sign of the antitumor effect of PD-1 inhibitors in those patients. However, CRS can be a fatal adverse effect and clinicians must remain vigilant for the rare toxicities to make prompt diagnosis and treatment.

KEYWORDS
cytokine release syndrome, *EGFR* mutation, NSCLC, pembrolizumab

INTRODUCTION

Pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, can reactivate the activity of exhausted CD8+ T cells and exert an antitumor effect; pembrolizumab has been approved and is widely used for the treatment of advanced non-small-cell lung cancer (NSCLC) lacking sensitizing *EGFR* or *ALK* mutations.[1,2] Evidence regarding the efficacy of PD-1 inhibitors in *EGFR*-mutated NSCLC is conflicting. A preclinical study revealed that *EGFR*-mutated lung tumors inhibit antitumor immunity by activating the PD-1/programmed-death ligand 1 (PD-L1) pathway and respond to anti-PD-1 therapies.[3] Several clinical studies have also demonstrated that changes in the tumor microenvironment in *EGFR*-mutated NSCLC following epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy may provide clues concerning the optimization of subsequent PD-1 inhibitor treatment.[4] Based on these findings, PD-1 inhibitors may benefit certain patients who are resistant to EGFR-TKIs. However, biomarkers to predict efficacy in these patients remain unclear.

Cytokine release syndrome (CRS) induced by immune checkpoint inhibitors (ICIs) has drawn clinicians' attention in recent years.[5] CRS is most reported in T-cell-engaging immune therapies, such as chimeric antigen receptor T-cell therapies,[6] and is rarely reported in patients receiving ICI therapy. Based on the analysis of the World Health Organization global pharmacovigilance database, the incidence of ICI-related CRS is approximately 0.07%.[7] CRS is defined as a systemic inflammatory response resulting from massive

TABLE 1 Laboratory test results on days 0, 8, 10, 12, and 20

	Day 0	Day 8	Day 10	Day 12	Day 20	Normal range
Complete blood count						
White blood cell	12 900	17 500	16 500	10 400	9900	3500–9500 (μL)
Hemoglobin	9.5	9.3	8.1	7.9	9.1	11.5–15.0 (g/dL)
Platelet	11.6	8.2	8.9	7.8	14.9	12.5–35.0 ($\times 10^4$/μL)
Lymphocyte	1300	7500	4600	3500	2100	1100–3200 (μL)
Biochemistry						
ALT	12	209	154	143	76	7–40 (U/L)
AST	25	592	293	204	84	13–35 (U/L)
TBIL	0.40	0.58	0.46	0.47	0.53	0.10–1.17 (mg/dL)
LDH	272	959	595	499	346	120–245 (U/L)
Creatinine	1.44	1.60	1.11	1.03	0.84	0.49–1.50 (mg/dL)
BUN	0.36	0.59	0.62	0.54	0.29	0.10–0.40 (mg/dL)
CRP	5.3	5.7	2.2	0.9	0.7	<0.3 (mg/dL)
Coagulation						
PT	12	15	12	11	10	10.1–12.6 (s)
D-dimer	8	11	7.3	6.9	3.6	<0.24 (mg/mL)
Fibrinogen	340	70	120	150	240	200–400 (mg/dL)
Lymphocytes						
CD8 + T cells	–	5712	–	–	1209	220–1129 (μL)
CD4 + T cells	–	598	–	–	692	404–1612 (μL)
Cytokine						
TNF-α	–	–	42.8	–	33	<8.0 (pg/mL)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; PT, prothrombin time; TBIL, total bilirubin; TNF-α, tumor necrosis factor-α.

cytokine release by activating immune effector cells after any immune therapy.[8] Patients with CRS can present with fever, hypotension, and multiple organ dysfunction, the severity of which ranges from mild to life-threatening.[8] Interleukin (IL)-6, interferon (IFN)-γ, tumor necrosis factor-α (TNF-α), and other cytokines are upregulated during CRS.[9]

Here, we report a challenging case of a patient with advanced *EGFR*-mutated NSCLC who successfully responded to pembrolizumab therapy after EGFR-TKI resistance. However, the patient developed CRS after pembrolizumab initiation.

CASE PRESENTATION

A 67-year-old woman presented with chest pain in September 2018. She had been diagnosed with hypertension a dozen years ago. The patient received the chest computed tomography (CT) examination, which showed a lesion in the right upper lung with mediastinal lymph node enlargement. The patient was diagnosed with stage IV lung adenocarcinoma. Next-generation sequencing (NGS) indicated L747-P753 deletion of EGFR exon 19 and TP53 Exon8 mutation. No further alterations were detected in the anaplastic lymphoma kinase (ALK), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), and mesenchymal epithelial transition factor receptor (MET) genes by fluorescence in situ hybridization. The patient received first-line gefitinib (250 mg/day) therapy for 6 months. In April 2019, the patient developed progressive dyspnea and chest ultrasonography showed massive right-side pleural effusion. The patient discontinued gefitinib and began treatment with osimertinib (80 mg/day) as second-line therapy in May 2019. Meanwhile, the patient received indwelling pleural catheter treatment. Tumor cells were detected in the pleural effusion cell block, and the PD-L1 22C3 tumor proportion score was 80%. No further alterations except for EGFR Exon19 deletions were detected in the pleural effusion cell block based on EGFR amplification refractory mutation system–polymerase chain reaction (ARMS-PCR) and plasma ctDNA NGS analysis, therefore the patient discontinued osimertinib. The malignant pleural effusion was not controlled well. The patient could not tolerate chemotherapy due to an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 4. On June 5, 2019, 200 mg of pembrolizumab was added to her treatment regimen. On the day of pembrolizumab administration (day 0), she developed fever, nausea, vomiting, and chest pain. We considered the infection because the hypersensitive C-reactive protein

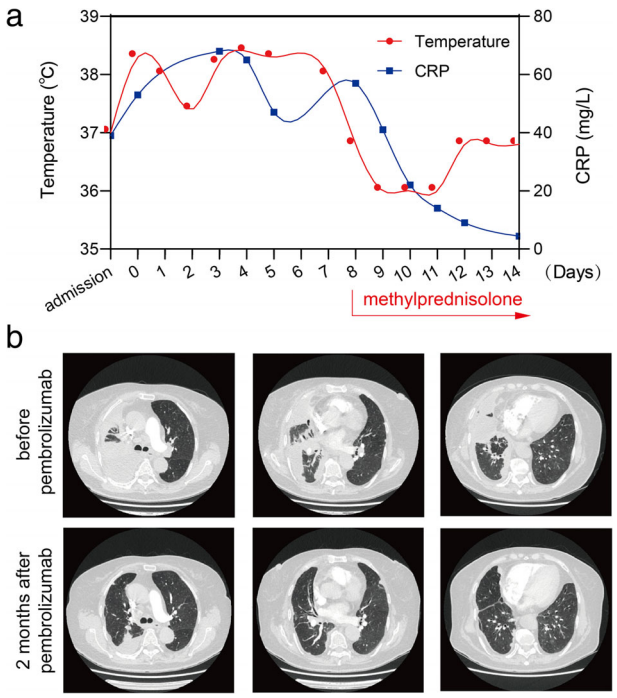

FIGURE 1 Clinical data and chest computed tomography (CT) imaging. (a) T_{max} and CRP levels after pembrolizumab treatment. On the *x* axis is the time of pembrolizumab infusion, on the left *y* axis is the daily maximum temperature (T_{max}) in degrees Celsius, and on the right *y* axis is C-reactive protein (CRP) levels. The horizontal arrow represents the time of initiating treatment with methylprednisolone. (b) Chest CT showing massive pleural effusion and atelectasis in the right lung on May 31, 2019 before pembrolizumab administration. By 2 months after pembrolizumab administration, significantly decrease of right-side pleural effusion and re-expansion of the right lung were observed

(hsCRP) and procalcitonin slightly elevated. However, empirical antibiotics did not control the patient's symptoms. On day 8, the patient experienced sudden hypotension, hypoxemia, tachycardia, and rash. Laboratory examination showed transaminase elevation, acute kidney injury, and disseminated intravascular coagulation. The laboratory test results are presented in Table 1. Blood cultures were negative, which excluded common bacterial infections. The number of T cells and serum cytokine levels, including TNF-α and hsCRP, were significantly elevated (Table 1). CRS was suspected and was categorized as grade 2 according to the American Society for Transplantation and Cellular Therapy grading system. In addition to fluid infusion and oxygen supplementation, methylprednisolone (100 mg/day) was administered from day 8 after pembrolizumab administration for 3 days. On day 9, the patient's temperature returned to normal (Figure 1(a)) and all other symptoms improved. Laboratory test results also gradually returned to normal, including CD8+ T-cell counts (Table 1).

The prednisolone dose was gradually tapered off in 2 weeks. The performance status of the patient improved, and the ECOG-PS score decreased from 4 to 1. The patient was discharged from the hospital on July 4, 2019. The patient refused to continue receiving pembrolizumab or other antitumor therapy for fear of adverse events during the follow-up period. Surprisingly, chest CT in August 2019 showed that the pleural effusion had decreased significantly (Figure 1(b)). Unfortunately, the patient died eventually due to progression of right lung lesions and brain metastases in November 2019, which was before the COVID-2019 pandemic in Beijing, China.

DISCUSSION

Salvage therapy options for *EGFR*-mutated NSCLC after EGFR-TKI resistance are a clinical challenge. The current patient received pembrolizumab after EGFR-TKI resistance due to intolerance to chemotherapy and showed a dramatic clinical response. The satisfactory outcomes may be explained by several reasons. First, the PD-L1 expression level and tumor mutation burden might increase after EGFR-TKI treatment and are associated with a better response to pembrolizumab.[4] Second, CD8+ T cells and inflammatory cytokines, such as TNF-α and C-reactive protein (CRP), increased early after pembrolizumab initiation, which showed an immune response to pembrolizumab. Previous studies have demonstrated that increased CD8+ T cells and inflammatory cytokines in peripheral blood after anti-PD-1 therapy initiation might predict positive clinical outcomes.[10,11] However, the threshold for the absolute lymphocyte count which could predict efficacy of immunotherapy is inconclusive. The case was notable for the presence of CRS, which is a systemic inflammatory response resulting from massive cytokines released by activating immune effector cells, including CD8+ T cells. CRS might reflect the degree of immunity activation and could be as a predictor of the response to PD-1 inhibitors in patients with EGFR-TKI resistance.

CRS is a newly reported ICI-induced adverse effect mediated by multiple cytokines, including IL-6, TNF-α, IFN-γ, IL-2, IL-8, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF), among which IL-6 has been suggested as the key protagonist.[8] CRP is thought to be a reliable surrogate marker for IL-6.[12] In the present case, CD8+ T cells and possibly other immune cells hyperactivated after receiving pembrolizumab released excessive cytokines, leading to CRS occurrence. Although the cytokines were not measured before glucocorticoid administration, the increase in CRP and TNF-α levels and response to glucocorticoids supported a diagnosis of CRS.

CRS incidence is related to disease burden, baseline cytokine level, and type of immunotherapeutic drugs. Because of the patient's high tumor burden, our patient might have been at a particularly elevated risk of CRS. In addition, EGFR-TKI has been demonstrated to downregulate regulatory T cells, which might cause the patient to be prone to immune-hyperactivation-induced damage.[13] Therefore, osimertinib might put patients at a high risk of CRS incidence. The patient's symptoms improved rapidly after treatment with glucocorticoids. In clinical practice, clinicians can choose tocilizumab (IL-6 receptor targeting monoclonal antibody) when glucocorticoid monotherapy cannot control the disease.[14]

In conclusion, pembrolizumab might be effective in some patients with advanced *EGFR*-mutated NSCLC after EGFR-TKI resistance. The number of CD8+ T cells in the peripheral blood, as well as the CRS phenomenon, would be a sign of clinical outcomes. However, CRS could be life-threatening, particularly in patients with a high disease burden simultaneously treated with EGFR-TKI. Clinicians should remain vigilant for CRS incidence and make prompt diagnosis and management.

ETHICS STATEMENT

The patients provided written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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CONFLICT OF INTEREST

All the authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

M.Z. conducted the medical literature search, constructed the table and figure, and drafted the manuscript. Y.C. assisted in revision of the manuscript as well as the associated table and figure. Y.H. and L.N. provided patient care and interpreted the data. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ORCID

Meng Zhang https://orcid.org/0000-0002-7130-3354
Yuan Cheng https://orcid.org/0000-0002-9763-7424

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