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

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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 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
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. 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

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**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 (×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.
However, the threshold for the CRP is thought to be
Therefore, osimertinib might
In the present case,
to continue receiving pembrolizumab or other antitumor
ECOG-PS score decreased from 4 to 1. The patient was dis-
Supplementation, methylprednisolone (100 mg/day) was
American Society for Transplantation and Cellular Therapy
suspected and was categorized as grade 2 according to the
and hsCRP, were significantly elevated (Table 1).
were not measured before glucocorticoid administra-
to pembrolizumab. Previous studies have demonstrated that
CRS was
and are associated with a better response to pembrolizumab. Second, CD8+$^+$ T cells and inflammatory cytokines, such as
T-cell counts (Table 2).
and type of immunotherapeutic drugs. Because of
the ECOG-PS score decreased from 4 to 1. The patient was dis-
continue receiving pembrolizumab or other antitumor
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. 
Second, CD8+$^+$ T cells and inflammatory cytokines, such as
TNF-$\alpha$ 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. 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 pre-
dictor of the response to PD-1 inhibitors in patients with
EGFR-TKI resistance.

**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
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EGFR-TKI resistance.

**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
On day 8, the patient experienced sudden hypotension, hyp-
oxemia, 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 nega-
tive, which excluded common bacterial infections. The num-
ber of T cells and serum cytokine levels, including TNF-$\alpha$
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 administra-
tion 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 dis-
charged 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.
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.

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