ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 December 26; 9(36): 11122-11508

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Thrice Monthly Volume 9 Number 36 December 26, 2021

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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
December 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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ONLINE SUBMISSION
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World J Clin Cases 2021 December 26; 9(36): 11419-11424

DOI: 10.12998/wjcc.v9.i36.11419

ISSN 2307-8960 (online)

CASE REPORT

Dramatic response to immunotherapy in an epidermal growth factor receptor-mutant non-small cell lung cancer: A case report

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Author contributions: Li D and Cheng C gave medical assistance to the study population and collected the data; Song WP, Wu X and Ni PZ analyzed the data; Li D wrote the draft of the manuscript; Zhang WZ and Wu X reviewed all versions of the manuscript and helped to shape it up; all authors contributed to the article and approved the submitted version.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Supported by Henan Provincial Science and Technology Research Project, No. 202102310157; Medical

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Abstract

BACKGROUND

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the management of several types of solid cancers, including lung cancer, by boosting the body's natural tumor killing response. However, it is undeniable that only a small proportion of non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations can achieve long-term responses and benefit from immunotherapy.

CASE SUMMARY

Herein, we report the case of a 48-year-old man diagnosed with stage IV lung adenocarcinoma with an EGFR L858R mutation who was administered pembrolizumab monotherapy followed by pemetrexed and achieved a 10-month progression-free survival interval. In this case report, we show that ICIs were effective for our patient with EGFR-mutated NSCLC and discuss the characteristics of patients who can benefit from immunotherapy.

CONCLUSION

We suggest that patients with EGFR-mutated NSCLC with high PD-L1 expression

Science and Technology Research Plan (Joint Construction) Project of Henan Province, No. LHGJ20190676.

Country/Territory of origin: China

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

Received: July 4, 2021
Peer-review started: July 4, 2021
First decision: September 28, 2021
Revised: September 29, 2021
Accepted: November 18, 2021
Article in press: November 18, 2021
Published online: December 26, 2021

P-Reviewer: Abed A, Batyrbekov K, Brat K, Konala VM, Sugimura H
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

(defined as ≥ 25%), the L858R mutation, smoking history, or pemetrexed pre-treatment may benefit from immunotherapy.

Key Words: Epidermal growth factor receptor mutation; Non-small cell lung cancer; Pemetrexed; Immunotherapy; Case report

Core Tip: In this paper, we report a patient with metastatic epidermal growth factor receptor-mutant non-small cell lung cancer showed dramatic response to immunotherapy after pemetrexed plus carboplatin and achieved a durable disease control over 10 mo. We aimed to analyze the potential reasons why the patient can benefit from immunotherapy and explore the strategy that should be adopted in the future.

Citation: Li D, Cheng C, Song WP, Ni PZ, Zhang WZ, Wu X. Dramatic response to immunotherapy in an epidermal growth factor receptor-mutant non-small cell lung cancer: A case report. *World J Clin Cases* 2021; 9(36): 11419-11424
URL: https://www.wjgnet.com/2307-8960/full/v9/i36/11419.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i36.11419

INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) can significantly prolong the median progression-free survival (PFS) benefit with very manageable toxicity profiles in advanced non-small cell lung cancer (NSCLC) patients harboring sensitive EGFR mutations. However, although this strategy is effective, the treatment response lacks durability, and disease progression frequently occurs after a median of 10 mo to 14 mo of EGFR-TKI therapy[1]. When resistance develops, systemic chemotherapy is administered as a second-line treatment following standard medical instructions for patients without T790M-positive NSCLC[2]. After the standard first- and second-line treatments, there are no effective strategies for the third-line therapy or beyond that improve patient overall survival outcomes. Immune checkpoint inhibitors, particularly inhibitors of the programmed death-1 (PD-1)/PD-ligand 1 pathways, have led to substantial modifications of NSCLC treatment strategies[3]. However, patients with metastatic EGFR-mutated NSCLC show a poor response to anti-PD-1/PD-L1 treatment[4]. In this paper, we report the case of a patient with metastatic EGFR-mutant NSCLC who showed a good response to immunotherapy after a dramatic response to gefitinib and pemetrexed plus carboplatin and achieved durable disease control over 10 mo. We aimed to analyze the potential reasons why patients benefit from immunotherapy and explore the therapeutic strategy that should be adopted in the future.

CASE PRESENTATION

Chief complaints

A 48-year-old man without a history of active or passive smoking presented to our hospital complaining of intermittent cough, bloody sputum, and chest pain in November 2017.

History of present illness

The patient had intermittent cough, bloody sputum, and chest pain for 1 wk.

History of past illness

The patient had no history of smoking and no underlying disease.

Personal and family history

He had no personal or family history of other diseases.

Physical examination

For physical examination, the patient presented with intermittent cough, bloody sputum and percussion pain in the chest area (+).

Laboratory examinations

His blood count showed a WBC of 8.23 × 10^9/L, neutrophil count of 2.12 × 10^9/L, Hb of 125 g/L, and platelet count of 210 × 10^9/L.

Imaging examinations

A chest computed tomography scan showed a nodule sized 57 mm × 52 mm, pleural infiltration, and mediastinal lymphadenopathy; therefore, surgery was not indicated (Figure 1A).

FINAL DIAGNOSIS

Subsequently, bronchoscopic biopsy suggested the diagnosis of adenocarcinoma. The EGFR exon 21 L858R mutation (with an abundance of 31.5%) was detected by droplet digital polymerase chain reaction of the biopsy sample. Finally, the patient was diagnosed with stage IV lung adenocarcinoma with pleural involvement harboring the EGFR exon 21 L858R mutation.

TREATMENT

After 11 mo of gefitinib (250 mg once daily) as the first-line treatment, his disease progressed without evidence of an EGFR T790M mutation (Figure 1B). Then, the patient received four cycles of pemetrexed (500 mg/m^2) plus carboplatin (at the target AUC = 5) and achieved a partial response (Figure 1C).

However, after 5 cycles of maintenance treatment with pemetrexed alone, the primary lung lesion enlarged, and the patient was found to have progressive disease (Figure 1D). Hence, pembrolizumab alone was applied at a dose of 200 mg every three weeks and was well tolerated without grade 3 or 4 adverse events during the treatment. After 4 cycles of treatment, a partial response was achieved and was maintained for 10 mo. However, the nodule in the lung enlarged and increased slightly after 14 cycles of pembrolizumab treatment.

OUTCOME AND FOLLOW-UP

The patient inevitably experienced disease progression and received anlotinib (12 mg once daily on days 1-14 of a 21-d cycle) as the fourth-line treatment in May 2020. The treatment timeline of this NSCLC patient is summarized in Figure 2.

DISCUSSION

In recent decades, PD-1/PD-L1 inhibitors, such as pembrolizumab and nivolumab, have been approved worldwide as treatments for advanced NSCLC and have been hailed as an important addition to the management of this patient population. The results of several phase III trials revealed that immune checkpoint inhibitors provide long-term survival benefits over chemotherapy for patients with advanced NSCLC[5-8]. However, a pooled analysis designed to compare several checkpoint inhibitors with traditional chemotherapy indicated that patients with EGFR-mutated NSCLC obtained no survival benefit from PD-1/PD-L1 inhibitors compared with that achieved with single-agent chemotherapy[9]. Mechanistic and additional confirmatory studies are ongoing. However, potential reasons for this lack of survival benefit have been proposed based on the role of EGFR in tumor cells and the effects of EGFR on immunologic effector cells. Regulatory T cells, which account for the main characteristics of tumors, play an important role in maintaining peripheral tolerance. EGFR signaling pathway activation can promote the generation of regulatory T cells *via* amphiregulin acting as a ligand of EGFR[10-12]. Nevertheless, EGFR signaling pathway activation can also promote the generation of tolerogenic dendritic cells to

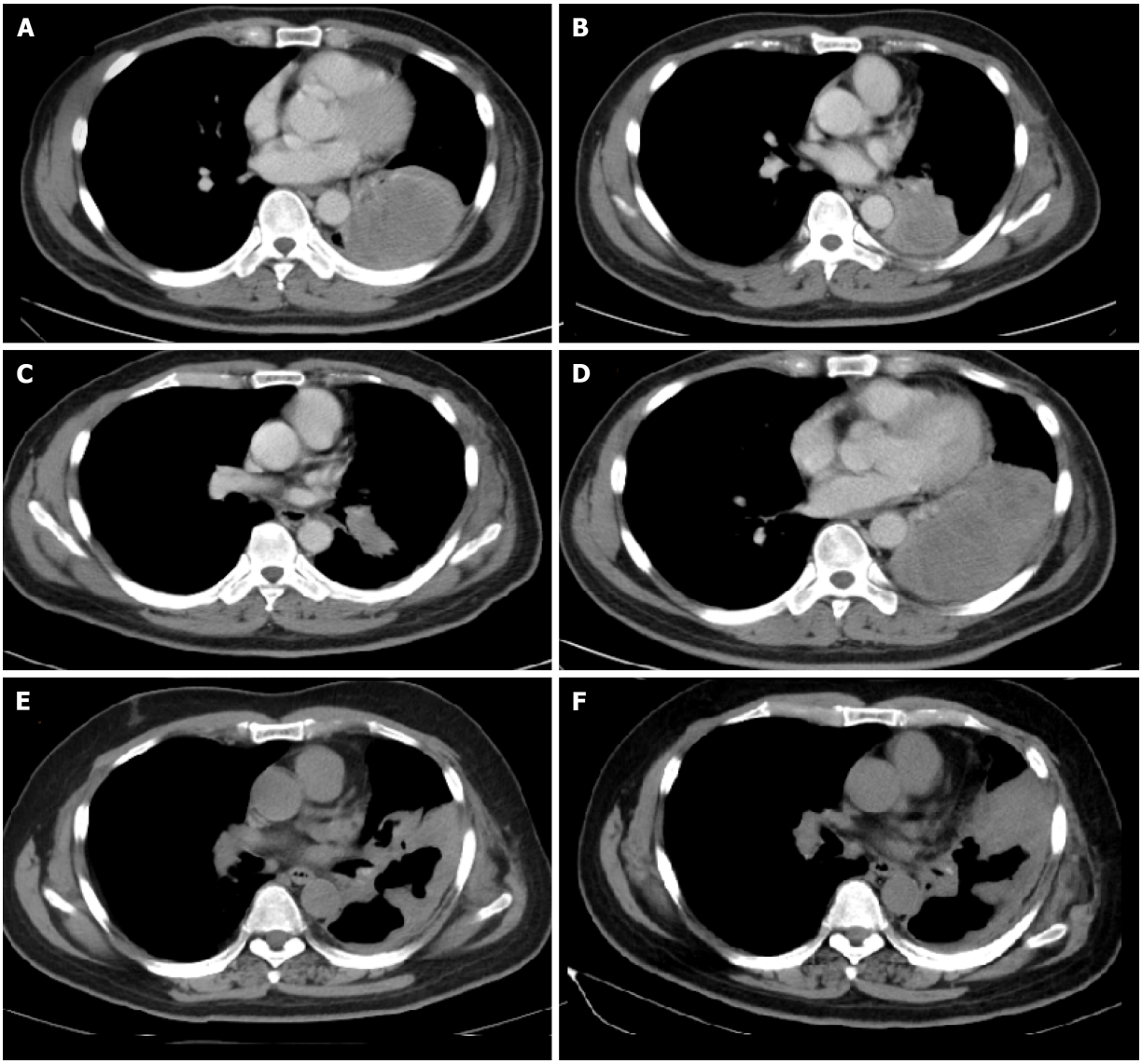

Figure 1 Computed tomography imaging of the non-small cell lung cancer patient. A: Computed tomography imaging showed the mass located in lower lobe of left lung before gefitinib treatment; B: The mass enlarged and increased slightly after 11 mo of gefitinib treatment; C; The mass shrank significantly after treated with 2 cycles of pemetrexed plus carboplatin; D: The mass enlarged sharply after treated with 5 cycles of pemetrexed; E: The mass shrank significantly during pembrolizumab treatment; F: The mass enlarged and increased slightly after 10 mo of pembrolizumab treatment.

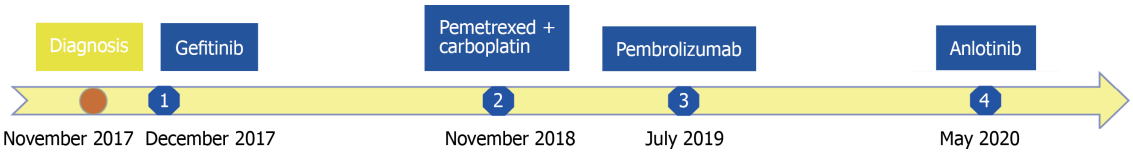

Figure 2 Timeline of events since the diagnosis and summary of administered treatments.

maintain immune tolerance *via* the negative selection of autoreactive T cells[13]. The activation of STAT3, an important downstream signaling molecule of the EGFR signaling pathway, plays an important role in the immune suppression of myeloid-derived suppressor cells to promote myeloid-derived suppressor cell-mediated immune suppression in lung cancer[14].

Most patients with NSCLC and EGFR mutations do not benefit from immunotherapy. However, based on the result of the ATLANTIC phase 2 clinical trial, patients with EGFR-mutated NSCLC and PD-L1 expression ≥ 25% have encouraging outcomes with an objective response rate (ORR) of 14.1% with durvalumab monotherapy, while EGFR-mutated NSCLC patients with PD-L1 expression < 25% showed a substantially lower ORR of 3.6%[15]. Additionally, the results of a multicenter, retrospective study

showed that patients with the L858R mutation achieved a comparable ORR to those with wild-type EGFR (7 of 44, 16%, *vs* 47 of 212, 22%, respectively, $P = 0.42$), while patients with the 19 exon deletion showed a lower response rate than those with wild-type EGFR (5 of 76, 7% *vs* 47 of 212, 22%, respectively, $P = 0.002$). However, whether the different tumor mutation burdens could be the cause of the various efficacies of immunotherapy in patients in terms of the subtypes of EGFR mutations remains uncertain[16]. There is no definitive conclusion on the correlation between clinical factors, such as smoking history or duration of response to prior target therapy, and the survival outcomes of patients receiving immunotherapy[17]. However, it is undeniable that a small proportion of patients with EGFR mutations could benefit from immunotherapy[18]. Further studies into the heterogeneity of EGFR-mutated tumors are needed to enhance the benefits and uses of PD-L1 therapies for patients with these mutations.

Meanwhile, Cavazzoni *et al*[19] indicated that only pemetrexed could increase PD-L1 Levels by activating both mTOR/P70S6K and STAT3 pathways and induce the secretion of cytokines by activated peripheral blood mononuclear cells, which further stimulated the expression of PD-L1[19]. Therefore, according to the results of previous studies, EGFR-mutated NSCLC patients with high PD-L1 expression (defined as ≥ 25%), the L858R mutation, smoking history, or pemetrexed pretreatment may benefit from immunotherapy. Thus, deeper study of these patients may help discover new therapeutic strategies for EGFR-mutated lung cancer patients.

Herein, we report a metastatic NSCLC patient with TKI-resistant EGFR-mutated tumors who progressed after systemic chemotherapy, benefited from pembrolizumab treatment, and achieved a ten-month PFS interval with a very manageable toxicity profile.

CONCLUSION

Consistent with the data in published reports, our case report also suggests that EGFR-mutated NSCLC patients with high PD-L1 expression (defined as ≥ 25%), the L858R mutation, smoking history, or pemetrexed pretreatment may benefit from immunotherapy, and they should not be excluded from trials or clinical applications of immune checkpoint inhibitors when resistance to TKIs or chemotherapy occurs. Furthermore, more research is needed to determine the subgroup of EGFR-mutated lung cancer patients who may benefit the most from immunotherapy.

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