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CASE REPORT

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Pembrolizumab and chemotherapy in non-small cell lung cancer with EGFR ex20ins mutation: A case report

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Abstract

The efficacy of immunotherapy in non-small cell lung cancer (NSCLC) with uncommon epidermal growth factor receptor (*EGFR*) mutations is not well clarified, even though immunotherapy has brought revolutionary improvements in *EGFR* wild-type NSCLC. In addition, pseudoprogression has increased the difficulty in immunotherapy management and data on the incidence of pseudoprogression in patients with EGFR exon 20 insertions (ex20ins) is rarely reported. Here, we discuss the case of an advanced lung adenocarcinoma patient with *EGFR* ex20ins alteration. The patient received pembrolizumab plus chemotherapy as first-line therapy and disease control was achieved. Progression-free survival (PFS) was 9 months. The patient was subsequently treated with pembrolizumab plus docetaxel and bevacizumab as second-line therapy and the disease remained stable. After two cycles of first-line treatment, the patient showed improvement in performance and the primary left upper lung lesion was stable; however, there was an increase in size as well as number of small diffuse bilateral pulmonary nodules. Therapy was maintained with the original regimen and complete regression of the bilateral lung nodules was achieved after a third cycle of treatment. Pseudoprogression was diagnosed. In the case reported here, we advocate the use of a PD-L1 inhibitor plus conventional chemotherapy in advanced NSCLC patients harboring EGFR ex20ins mutation and hope that our experience might be beneficial to other clinicians in distinguishing pseudoprogression from true progression.

KEYWORDS

chemotherapy, *EGFR* ex20ins mutation, NSCLC, pembrolizumab, pseudoprogression

INTRODUCTION

Non-small cell lung cancer (NSCLC) patients harboring *EGFR* ex20ins mutation have a poor prognosis due to insensitivity to EGFR TKI therapy, and treatment with traditional chemotherapy is recommended.[1] In the era of immunotherapy, PD-1/PD-L1 inhibitors are increasingly used in NSCLC.[2] Although the efficacy of immunotherapy in patients with common *EFGR* mutants is unfavorable,[3] a clinical trial demonstrated that immunotherapy may be beneficial in NSCLC harboring *EGFR* ex20ins mutation.[4] However, there is still no evidence to verify the efficacy of chemotherapy with the addition of immunotherapy in those patients. Meanwhile, the specific response pattern-pseudoprogression poses a huge challenge in deciding when to discontinue immunotherapy. Pseudoprogression is defined as an increase in tumor size or the appearance of new lesions in the initial stages of immunotherapy, with subsequent regression.[5] The incidence of pseudoprogression in NSCLC patients receiving immunotherapy has previously been reported as 1.81%–5.77%.[6] However, there is no available data on the epidemiology of pseudoprogression in patients with *EGFR* ex20 ins mutation. In addition, pseudoprogression mostly occurs after immune checkpoint inhibitor (ICI) monotherapy, and is rarely reported after being treated with a combination of ICIs and chemotherapy. Here, we report a case of advanced NSCLC

with *EGFR* ex20ins mutation in a patient who subsequently developed pseudoprogression after pembrolizumab plus chemotherapy. In addition, we also discuss the efficacy of immunotherapy plus chemotherapy in those patients.

CASE REPORT

A 40-year-old male with a smoking history presented with progressive sacral pain in January 2020. Magnetic resonance imaging (MRI) showed a 7.7 × 2.2 × 5.6 cm mass in the sacrum. Biopsy of the sacrum revealed bone metastases from lung adenocarcinoma. Chest computed tomography (CT) showed a lesion in the left upper lung and multiple nodules in bilateral lungs (Figure 1(a)). Multiple metastases in the mediastinal lymph nodes and bone were also present. A clinical stage of T4N3M1 (stage IV) lung adenocarcinoma was confirmed. The patient had a PD-L1 tumor proportion score (TPS) of 2% (22C3). Next-generation sequencing (NGS) of tumor tissue showed *EGFR* ex20ins mutation (Ser768_Asp770dup, mutant allele frequency [MAF], 85.16%) and TP53 mutation (MAF, 86.09%). He was treated with pembrolizumab plus pemetrexed and carboplatin therapy every 3 weeks as first-line therapy from June 2020 and received concurrent palliative radiation therapy (30Gy/10f/2w) for sacral metastases. After two cycles of therapy, the patient's performance had improved with a stable left upper lung mass, but the size and number of small diffuse bilateral lung nodules had increased (Figure 1(b)). We examined the tumor markers and found a sharp decrease in the serum carcinoma embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels. The patient continued to be treated with pembrolizumab combined with pemetrexed and carboplatin. After the third cycle of therapy, a chest CT scan showed complete regression of the diffuse pulmonary small nodules, with a stable lesion in the left upper lobe (Figure 1(c)). During first-line therapy, disease control was achieved in the patient with progression-free survival (PFS) of 9 months. In March 2021, the lesion and tumor markers in the left upper lung were found to have increased (Figure 1(d)). Transbronchial lung biopsy was subsequently performed and tumor progression was confirmed. NGS of tumor tissue showed the same *EGFR* ex20ins mutation as the first biopsy. Since then, the patient has received pembrolizumab plus docetaxel and bevacizumab every 3 weeks from March 2021 and the disease remains stable (Figure 2). The patient has been regularly followed up to July 2021.

Written informed consent to publish the case details was obtained from the patient.

DISCUSSION

EGFR exon 20 insertions (EGFR ex20ins) are an uncommon *EGFR* mutation type, accounting for about 0.1% to 4% of all cases of NSCLC.[7] The median PFS in these patients has been reported to be only 2 months (95% CI: 0.00–5.41).[1,8,9] Several clinical trials have been conducted in order to find an effective regimen for this population.[10–12] However, chemotherapy is still considered the most suitable treatment strategy in these patients.[13] At the same time, a clinical trial has demonstrated that NSCLC harboring *EGFR* ex20ins had a higher PD-L1 expression, which indicates that those patients might benefit from PD-1/PD-L1 inhibitors.[4] In clinical practice, some clinicians have previously reported that NSCLC patients achieved disease control after receiving pembrolizumab with/without chemotherapy.[14,15] In our case, the patient was diagnosed with advanced lung

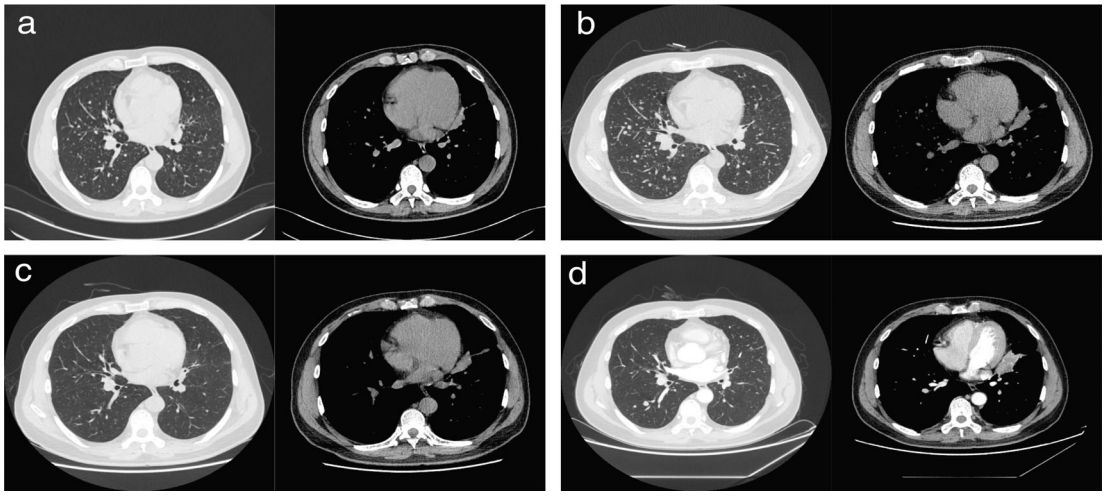

FIGURE 1 Chest computed tomography (CT) and follow-up CT images. (a) A lesion in the left upper lung with small diffuse bilateral pulmonary nodules and mediastinal lymphadenopathy before treatment. (b) Although the lesion in the left upper lung was stable, the size and number of small diffuse bilateral pulmonary nodules after two cycles of pembrolizumab plus chemotherapy had increased. (c) There was a further reduction in size and number of bilateral pulmonary nodules after three cycles of pembrolizumab plus chemotherapy. (d) Chest CT in March 2021 showed an increase in size of the lesion in the left upper lung

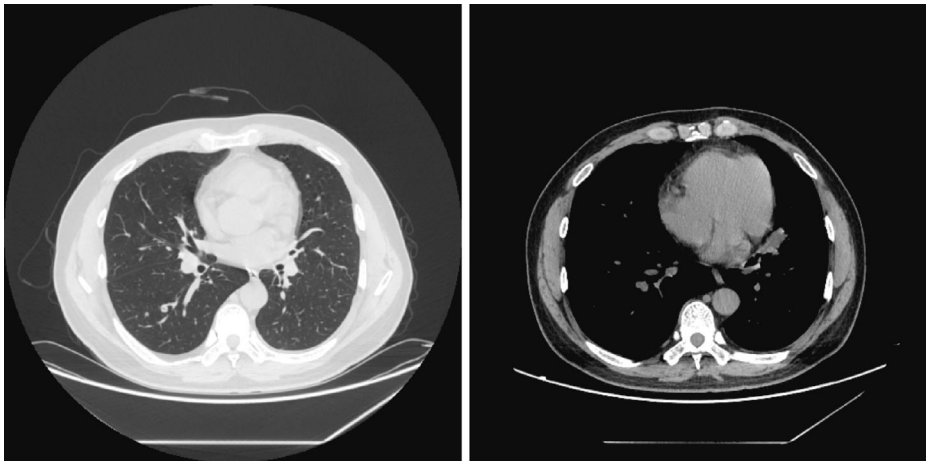

FIGURE 2 Chest computed tomography (CT) showed a stable lesion in the left lung and bilateral pulmonary nodules after receiving pembrolizumab plus docetaxel and bevacizumab

adenocarcinoma with *EGFR* ex20ins mutation and PD-L1-positive tumors. He was treated with pembrolizumab plus pemetrexed and carboplatin as first-line therapy and disease control was achieved with PFS reaching 9 months. It is exciting that the USA FDA approved amivantamab as second-line therapy in NSCLC with *EGFR* ex20ins mutations in May 2021. However, amivantamab is not available in China at present. Therefore, the patient received pembrolizumab plus docetaxel and bevacizumab as second-line therapy with stable disease until July 2021. After two cycles of first-line therapy, the size and number of bilateral lung nodules had increased. Pseudoprogression was suspected based on the performance improvement, primary lesion stabilization and decrease in tumor markers. With the completion of the third cycle of the same treatment, the size and number of bilateral lung nodules regressed and a diagnosis of pseudoprogression was made. The pseudoprogression may indicate a favorable reponse to immunotherapy in our case. Although pseudoprogression in cancer patients receiving ICI monotherapy is well known, it has rarely been reported in patients who have received immunotherapy plus chemotherapy, especially in patients with uncommon *EGFR* mutations. Pseudoprogression may be caused by necrosis, edema, or immune cell infiltration of the tumor,[16] but whether these changes occurred after receiving immunotherapy and chemotherapy remains unclear. Additionally, our case indicated that CEA may be useful in distinguishing pseudoprogression from real progression. However, the biomarkers for diagnosing pseudoprogression need to be explored further in the future.

In conclusion, NSCLC harboring *EGFR* ex20ins mutation management remains a challenge for clinicians. Immunotherapy combined with chemotherapy might be a potential treatment strategy, but should be confirmed in clinical trials. Additionally, pseudoprogression after immunotherapy combined with chemotherapy needs to be explored further in terms of its molecular mechanism.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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