

Case Report

Pembrolizumab is effective for a patient with extensive intracranial metastasis of non-small cell lung cancer poorly responsive to chemotherapy, radiotherapy, surgery and other targeting therapy: a case report

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Abstract: Here we reported a patient with advanced non-small cell lung cancer (NSCLC) that relapsed two times after resection of the tumor, chemotherapy, radiation therapy, and a targeting therapy during a disease course of nearly 4 years. In the second relapse, huge intracranial metastases occurred with symptoms such as severe headache, bedridden and dying feelings. After using the anti-programmed death-1 (anti-PD-1) antibody Pembrolizumab for 2 months, NSCLC disappeared completely and symptoms improved greatly at least for 6 months, indicating that anti-PD-1 antibody has great potential for treatment of NSCLC. In addition, antibodies targeting PD-1/PD-L1 checkpoint are safe and well tolerated.

Keywords: Non-small cell lung cancer, programmed death-1, immunotherapy, treatment, antibody

Introduction

Non-small cell lung cancer (NSCLC), accounting for 85% of all lung cancers [1], is one of the leading causes of cancer-related death worldwide [2]. There have been significant advances in treatment strategies over the past decade. However, the overall 5-year survival rate increased only slightly in the past ten years [3]. Recently, immunotherapies such as antibodies targeting the immune checkpoints have revealed excellent results in several types of cancers. Three new immune checkpoint agents have now been approved by U.S. FDA. The antibody against CTLA-4 Ipilimumab was approved in 2011, and two antibodies against programmed death-1 (PD-1) Pembrolizumab and Nivolumab were approved in 2014 [4]. Anti-PD-1 therapies Pembrolizumab and Nivolumab have been used for the treatment of melanoma with a higher remission rate. Here we reported a NSCLC patient getting excellent response to Pembrolizumab.

Case presentation

A 64-year-old man was admitted to the hospital on Aug. 2012 because of fever, chills, cough

and sputum for several weeks. Lung CT and positron emission tomography CT (PET-CT) revealed a nodule in right lung hilus with enlarged mediastinal and left supraclavicular lymph nodes (**Figure 1A**). Biopsy of a supraclavicular lymph node revealed cancer metastasis morphologically and immunohistochemically identified to be adenocarcinoma probably from lung cancer. Based on these clinical results, NSCLC was diagnosed and the clinical state was designed as TXN3M0 and stage IIIB.

The patient was then treated with chemotherapy, radiotherapy, and targeted therapy. He was first treated with chemotherapy of EP regimen (intravenous Etoposide 160 mg/day at day 1-13 combined with intravenous Cisplatin 120 mg at day 1, and 24 days as one cycle) for 4 cycles. After that, intravenous Alimta was given (850 mg every 21 days) for 12 cycles. Two months after the initial diagnosis, radiotherapy of 6MV X-ray irradiation on mediastinum, right hilar, and bilateral supraclavicular lymphatic drainage areas was used. Targeting agent Nimotuzumab (intravenous 400 mg/week for a total of 16 times) was used at the same time. After these therapies for about one year, the lung cancer and metastatic lymph nodes were re-

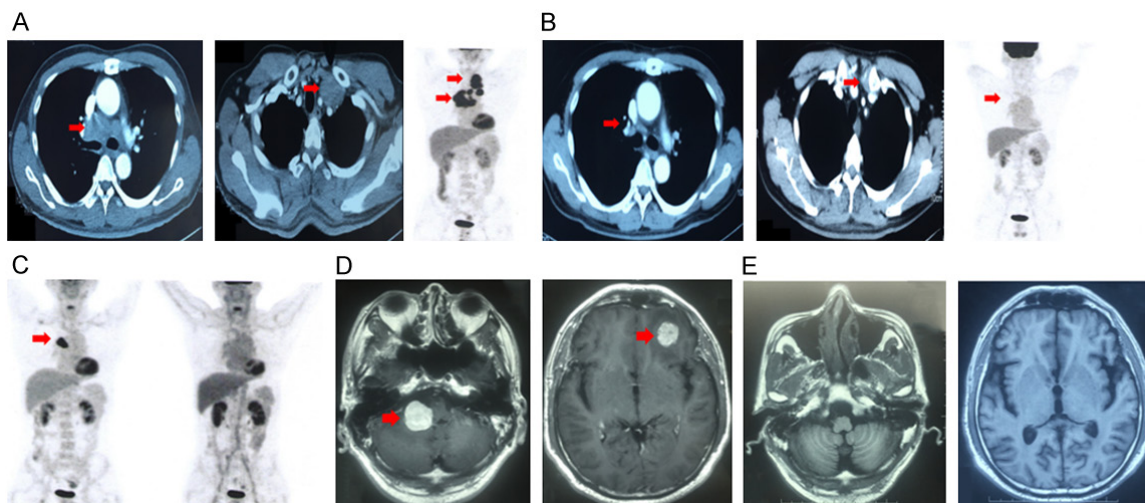


Figure 1. Chest CT, PET-CT and MRI images of the patient. A: Chest CT and PET-CT, a bulky lesion is found in right lung hilus with enlarged and irregular shaped cervical lymph nodes (red arrows); B: Chest CT and PET-CT, the tumor sizes in mediastinum and left supraclavicular lymph nodes decreased significantly after comprehensive treatments for about one year; C: PET-CT shows the first relapse of the tumor in right mediastinal lymph nodes, and after surgery and chemotherapy for the first relapse of the tumor for 9 months shows the size of hypermetabolic foci in mediastinum lymph nodes decreased but remained visible. D: Two metastatic tumors of diameters of 2.6 and 1.7 cm are found in right pons and left frontal lobe respectively on brain MRI on Oct. 2015. E: Metastatic tumors in brain disappear completely on Mar. 2016 after 4 doses of intravenous Pembrolizumab in 2 months.

duced significantly on CT scan and PET-CT images (**Figure 1B**).

After the treatments for one year on Oct. 2014, tumor relapsed in right mediastinal lymph nodes on PET-CT (**Figure 1C**). The patient underwent resection of right pulmonary wedge and mediastinal lymph nodes under thoracoscopic surgery. After the surgery, adjuvant chemotherapy including Docetaxel 130 mg and Cisplatin 130 mg at day 1 was conducted. The chemotherapy was terminated after 3 cycles.

During the period from May 2013 to Jun 2015, autologous dendritic cells-cytokine induced killer cells (DC-CIK) therapy was also used but without obvious effects. PET-CT after surgery and chemotherapy for the first relapse of the tumor for 9 months showed a small hypermetabolic focus in right mediastinum (**Figure 1C**).

A year after the first relapse on Oct. 2015, the second relapse of NSCLC emerged. He complained of dizziness, headache, nausea and vomiting, hearing loss of right ear, salivation of right side, and swallowing difficulties. Two metastatic foci with the diameters of 2.6 and 1.7 cm were detected in right pons and left frontal lobe respectively by brain MRI (**Figure 1D**). Serum ferritin increased to 1,152 ng/ml, serum

CA19-9 to 139.9 U/ml, and serum CA125 to 70 U/ml.

Two months after the second recurrence, intravenous Pembrolizumab 100 mg every 2 weeks was administered as a second-line treatment for relapsed NSCLC. After 4 doses of Pembrolizumab in 2 months, metastatic tumors in brain disappeared (**Figure 1E**) and no significant tumor images in mediastinal and supraclavicular sites were found in brain MRI and chest CT. Serum ferritin decreased from 1,152 to 486.2 ng/ml, serum CA19-9 from 139.9 to 36.6 U/ml, and serum CA125 from 70 to 28.5 U/ml. Symptoms associated with the brain tumors disappeared completely. No adverse events except mild and transient skin rashes were found, and his general condition improved greatly. He then discharged from the hospital after 4 doses of intravenous Pembrolizumab. The complete remission of the NSCLC persisted in the following 6 months.

Discussion

Here we reported a NSCLC patient with the clinical stage of IIIB. At first, he got complete remission of the tumor after combination of chemotherapy, radiotherapy, Nimotuzumab, Alimta and DC-CIK. After one year, however, the tumor

relapsed and mediastinal lymph nodes enlarged once again in right paratracheal position. No mutations in EGFR gene were detected in a biopsy sample from a metastatic lymph node. Conventional therapies for NSCLC such as chemotherapy, radiation and surgery are effective but cannot eradicate residual cancer cells completely in most cases. In this case, brain metastasis happened in the second relapse of NSCLC after the combination of several potent antineoplastic therapies. The patient was then used Pembrolizumab as a second-line treatment for NSCLC. Tumors in mediastinum, cervical lymph nodes, and brain disappeared completely, and the general condition of the patient improved greatly.

Recent researches indicated that the development of malignant tumors is closely correlated with the activation of PD-1 in most cases [9]. The ultimate amplitude and quality of the T-cell responses initiating through antigen recognition by T cell receptors are regulated by a balance between costimulators and co-inhibitors (the immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance to prevent autoimmunity and tissue damages when the immune system is responding to pathogenic infection or injuries [10, 11]. CTLA-4 and PD-1 play critical roles in T cell co-inhibition and exhaustion [12]. PD-1 and its ligands PD-L1 and PD-L2, deliver inhibitory signals to decrease T-cell activity and cytokine production from T-cells, induce apoptosis of tumor infiltrating lymphocytes, and modulate anti-tumor immune responses [13, 14]. Positive PD-L1 expression in primary cancer cells are closely correlated to immune escape of tumor cells [15]. The major function of PD-1 on tumor infiltrating lymphocytes is to limit T cell activity and induce their apoptosis through interaction with its ligand PD-L1 on tumor cells, resulting in repression of anti-tumor immunity [16, 17]. In conclusion, we report a NSCLC patient with extensive intracranial metastasis exhibiting excellent responses to anti-PD-1 monoclonal antibody Pembrolizumab, indicating that anti-PD-1 antibody has great potential for treatment of NSCLC.

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Disclosure of conflict of interest

None.

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