Long-term survival of a patient with advanced lung cancer treated with targeted therapy and anti-PD-1 immunotherapy as multi-line therapy: A case report

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Abstract. Lung cancer is the most common type of cancer worldwide. Lung adenocarcinoma, a type of non-small cell lung cancer (NSCLC), is a common type of lung cancer. In recent years, immunotherapy has become the primary method of treatment for several solid cancers, including NSCLC. In the present study, the case of a patient with NSCLC following left superior lobectomy is reported. Different systemic therapies failed, such as a pemetrexed + carboplatin regimen, paclitaxel liposome + cisplatin and pembrolizumab, and albumin-bound paclitaxel + toripalimab, but long-term survival was achieved following targeted therapy and anti-programmed cell death protein-1 (PD-1) immunotherapy. The patient survived for >4 years following lung cancer progression, which is notably longer than expected for patients with advanced lung cancer. In conclusion, the present case demonstrated the efficacy of targeted therapy and anti-PD-1 immunotherapy for the treatment of advanced lung cancer following the occurrence of drug resistance and progressive disease.

Introduction

Lung cancer is the most common type of cancer worldwide with an incidence rate of 11.4% and has a high mortality rate (number of deaths per year, 1,796,144) (1). Lung adenocarcinoma, a type of non-small cell lung cancer (NSCLC), is a common type of lung cancer (40 to 55% of total lung cancer cases) (2). The risk factors for the disease include long-term smoking, cooking fumes, air pollution and genetic factors.

Targeted therapy is based on the application of selective inhibitors and biomolecules, which can impair the growth of lung cancer cells via interference with specific targeted receptors or other downstream proteins, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), kirsten rat sarcoma viral oncogene (KRAS), v-raf murine sarcoma viral oncogene homolog B (BRAF), and human epidermal growth factor receptor 2 (HER-2) (3). Targeted therapy, including tyrosine kinase inhibitor (TKI)-based therapy, has been reported to improve the overall survival (OS) and quality of life of patients with NSCLC who have mutations (4). A meta-analysis of existing data reported that the EGFR single nucleotide polymorphisms rs712829 (-216g>T) and rs11568315 (CA repeat) significantly affected OS and progression-free survival (PFS) in patients with NSCLC who were treated with the TKIs gefitinib or erlotinib (4). However, another study reported that patients who were carriers of the long CA repeat (SL+LL) were more likely to experience skin toxicity associated with TKIs (5).

Targeted immunotherapy promotes the activation of the immune system against lung cancer cells (3). In contrast to non-immune checkpoint inhibitor (ICI) agents, such as pemetrexed and carboplatin, ICI agents have the potential to improve long-term survival, represented by a plateau at the tail of the survival curve in small patient populations for several cancer types, including melanoma (6). Programmed cell death 1 ligand 1 (PD-L1)-positive cases (≥1-49%) are recommended for the treatment, including carboplatin or cisplatin (7) combined with pemetrexed and pembrolizumab, or with carboplatin combined with paclitaxel, bevacizumab and atezolizumab according to the National Comprehensive Cancer Network guidelines (8); pembrolizumab (9) is also recommended by the European Society of Medical Oncology (2) and American Society of Clinical Oncology guidelines (10).

Platinum chemotherapy is the recommended first-line treatment for patients with advanced NSCLC without targeted

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gene mutations; however, the systemic toxic side effects (such as gastrointestinal reaction, hematological toxicity and impairment of liver and kidney function) and overall drug resistance to chemotherapy remain significant challenges (11). Moreover, when both drug resistance and progressive disease occur, the effectiveness of a number of chemotherapy drugs decreases. For example, the third-generation EGFR TKI, osetinib, was developed for the treatment of patients with NSCLC with T790M mutations. However, although it has demonstrated superiority over first- and second-generation EGFR-TKIs in high selection for EGFR-activating mutations as well as the T790M mutation, the development of drug resistance is still a limitation (12).

Targeted therapy combined with immunotherapy has become the primary treatment for several types of solid cancers, such as melanoma and lung and colorectal cancer, in the last 5 years (13). Programmed cell death protein 1 (PD-1) and PD-L1 inhibitors are types of ICI agents. Antibody blocking of PD-1 prevents its interaction with PD-L1 and PD-L2 by obstructing their downstream pathways and restoring the antitumor response of T cells (14). These are the most successful amongst all clinically applied checkpoint inhibitors. Anti-PD-1 immunotherapy provides a novel means of treating advanced lung cancer (3).

The present study reports the case of a patient with advanced NSCLC treated with targeted therapy and anti-PD-1 immunotherapy after multiple lines of failed therapies, providing further evidence for adopting targeted therapy and anti-PD-1 immunotherapy in the clinical treatment of advanced NSCLC.

Case report

A 60-year-old woman was admitted to the Affiliated Hospital of Nanjing University of Chinese Medicine (Nanjing, China) for a routine physical examination in September 2017. The patient was 168 cm tall and weighed 69 kg, with no medical history of chronic illnesses. The patient did not smoke, consume alcohol or recreational drugs, and had no notable family history of cancer. The patient provided written consent for the publication of their data.

A chest radiograph demonstrated a shadow in the left upper lung. The patient was subsequently admitted to the Department of Oncology, and the chest and abdomen were examined by enhanced computed tomography (CT) scan, which demonstrated peripheral lung cancer in the left upper lobe (Fig. 1). Bone emission CT (ECT) revealed that the radioactivity distribution of the spine (both systemic and local) was not uniform, and the radioactivity in local areas was slightly concentrated, with possible degeneration.

The patient was transferred for thoracic surgery at 13 days post-admission and underwent a video-assisted left upper lobectomy and lymphadenectomy. An interim diagnostic report of intraoperative frozen section pathology [freezing temperature, cryochamber temperature -23˚C, object temperature -21˚C; thickness of sections, 6 μm; hematoxylin and eosin staining (according to standard procedures); light microscope OLYMPUS BX43] showed that the left upper lung mass was an adenocarcinoma (characteristics of cytology: Lung adenocarcinoma cells typically exhibit circular or polygonal shapes, the nucleus is large and irregular, increased nuclear chromatin with patchy appearance, more mitotic figures. Formation of acini: Lung adenocarcinoma often forms acinar structures in the tissue, mucus secretion in the acini. Infiltrating growth: Lung adenocarcinoma can invade surrounding lung tissue and blood vessels and form clear boundaries of cancer tissue). The postoperative pathological examination (according to standard procedures) of the left upper lung mass resection specimen involving conventional histopathological and immunohistochemical staining (according to standard procedures) supported a diagnosis of lung adenocarcinoma that was moderately differentiated (acinar type, ~60%; adherent type, ~40%) with a size of 2x1.4x1 cm, with no definite vascular tumor thrombus and no nerve invasion. No cancer tissue was found at the cut ends of the hilum and bronchus, and 1 of the 2 lymph nodes demonstrated cancer metastasis (Fig. 2). Immunohistochemistry staining using an Optiview DAB IHC Detection Kit (Agilent Technologies, Inc.) was performed for thyroid transcription factor-1 (TTF-1; clone, 8G7G3/1), NapsinA (clone, IP64), ALK (clone, D5F3), cytokeratin (CK) 7 (clone, OV-TL 12/30), CK20 (clone, Ks 20.8) and Villin (clone, 1D2 C3). Ready-to-use antibodies, which were not diluted, TTF-1 and NapsinA were purchased from Beijing Zhongshan Golden Bridge Biological Technology Co., Ltd.; ALK was purchased from Ventana Medical Systems, Inc.; CK7, CK20 and Villin were purchased from Agilent Technologies, Inc. Standard procedures: i) Fixed solution, 10% neutral buffered formalin-fixed solution, fixed at room temperature for 6 to 24 h: Using immunohistochemical tissue anti-detachment tablets with a cross-sectional thickness of 3 μM; ii) sealing reagent, 3% hydrogen peroxide, room temperature, 10 min; iii) the following primary antibodies were used: TTF1 (ready to use; clone 8G7G3/1; cat. no. ZM-0250; OriGene Technologies, Inc.) and NapsinA (ready to use; clone IP64; cat. no. ZM-0473; OriGene Technologies, Inc.) incubated at 37˚C for 32 min; ALK (ready to use; clone D5F3; cat. no. 790-4794; Ventana Medical Systems, Inc.) incubated at 37˚C for 20 min; CK7 (ready to use; clone OV-TL 12/30; cat. no. M7018; Agilent Technologies, Inc.), CK20 (ready to use; clone Ks 20.8; cat. no. M7019; Agilent Technologies, Inc.) and Villin (ready to use; clone 1D2 C3; cat. no. IR076; Agilent Technologies, Inc.) incubated at room temperature for 40 min; iv) the following secondary antibodies were used: Optiview HRP Multimer (ready to use; cat. no. 760-700, Ventana Medical Systems, Inc., room temperature, 12 min), EnVision FLEX, EnVision FLEX/HRP (ready to use; cat. no. GV800, Agilent Technologies, Inc., room temperature, 20 min), with 25 ml OptiView Peroxidase Inhibitor (3.0% H_2O_2), 25 ml OptiView HQ Universal Linker (~50 μg/ml), 25 ml OptiView HRP Multimer (~40 μg/ml), 25 ml OptiView DAB (0.2% w/v DAB), 25 ml OptiView H_2O_2 (0.04% H_2O_2) and 25 ml OptiView Copper (5.0 g/l $CuSO_4$); v) DAB shows a positive result with a brownish yellow marker, while hematoxylin is used to contrast non-positive stained nuclei; and a vi) light microscope OLYMPUS BX43. Immunohistochemistry of the tumor cells demonstrated the following expression results: TTF-1(+), NapsinA(+++), ALK(-), CK7(+++), CK20(-) and Villin local(++). Paraffin tumor tissue detection gene testing was performed using next-generation sequencing (NGS) according to standard protocols (15,16), demonstrated that the G12D mutation in codon 12 of exon 2 of the KRAS gene (c.G35A, p.G12D)

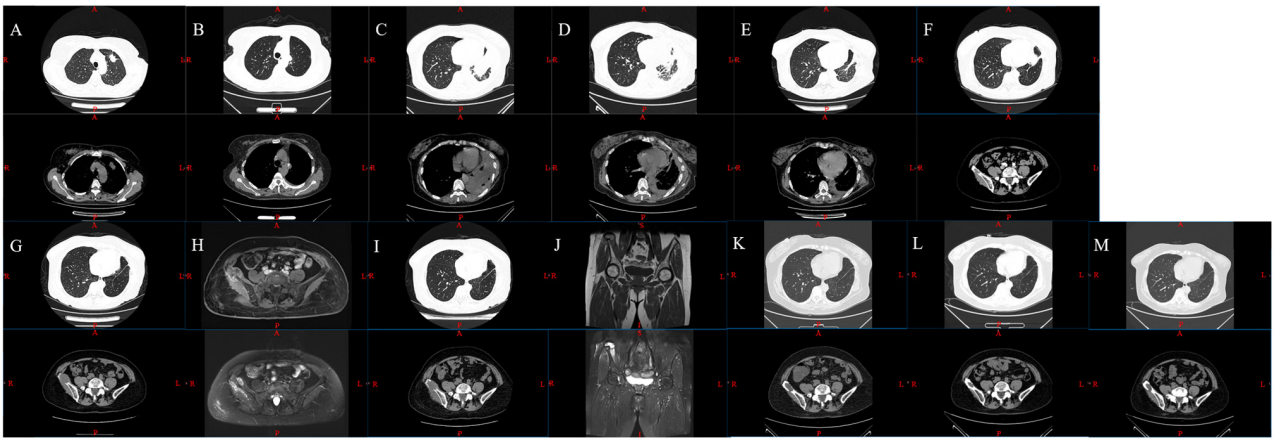

Figure 1. CT and MRI scans images. CT scans on (A) 2017-09, (B) 2017-10, (C) 2019-01, (D) 2019-03, (E) 2019-06, (F) 2019-11 and (G) 2020-02. MRI scan on (H) 2020-02, CT scan on (I) 2020-06, MRI scan on (J) 2020-08, and CT scans on (K) 2022-11, (L) 2023-03 and (M) 2023-07. CT, computed tomography; R, right; L, left; A, anterior; P, posterior; S, superjacent; I, inferior.

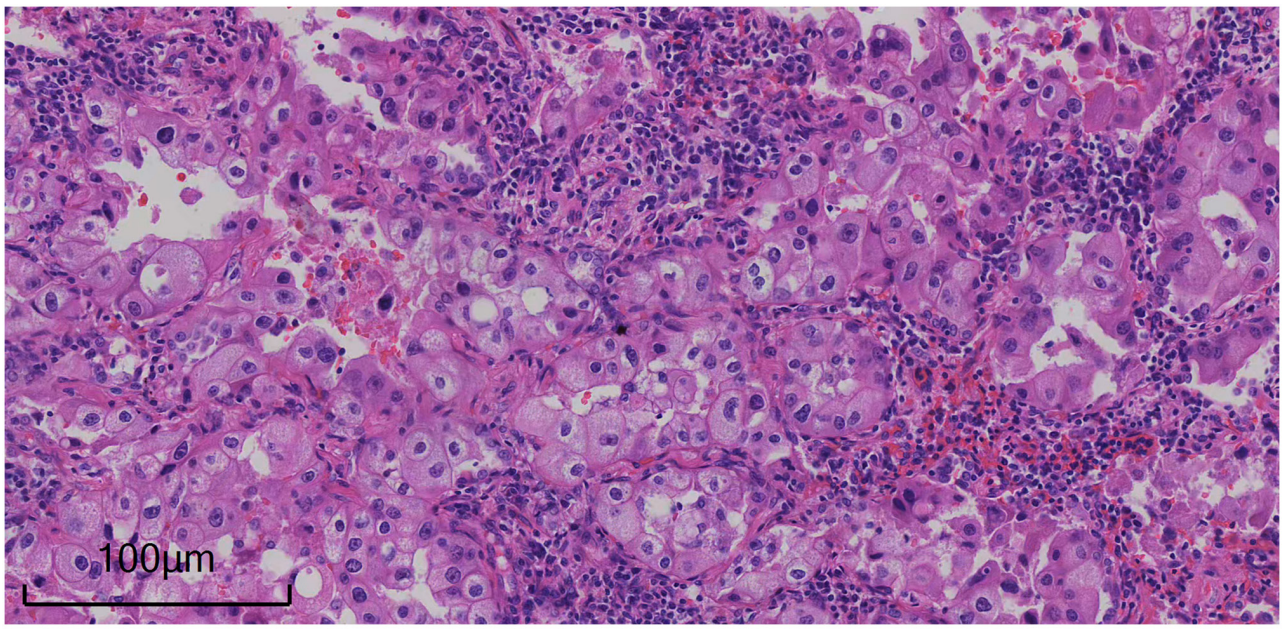

Figure 2. Pathological examination of the left upper lung mass resection specimen (hematoxylin and eosin staining).

had an abundance of 67.5%, while no mutations were found in genes such as EGFR, ALK, ROS1, BRAF, MET, HER-2, AKT1, MAP2K1 (MEK1), NRAS, NF1, PIK3CA, PTEN and RET. The clinical stage of the cancer was determined to be IIB according to AJCC Cancer Staging Manual (17). Body surface area (m^2) of the patient was calculated to determine correct dose by using the following formula: 0.0061 x height (cm) + 0.0128 x weight (kg) -0.1529. The patient received 6 cycles of a pemetrexed + carboplatin regimen as adjuvant chemotherapy (intravenous drip; 0.8 g pemetrexed on day 1+0.5 g carboplatin on day 2) from October 2017, to February 2018. The treatments received by the patient and the subsequent outcomes are listed in Table I.

In January 2019, the patient experienced notable chest pains with chest tightness and asthma. Left thoracic puncture drainage was performed, draining dark red liquid blood, which indicated disease progression. In February 2019, the patient experienced paroxysmal left lower chest pain after tiredness, and the underarm surgical wound exhibited a notable and needle-like pain. Chest CT demonstrated abundant pleural effusion on the left side, partial compression of the left lung showing consolidation and a left subpleural nodule shadow. This appeared to have progressed compared to the CT scan performed in September 2018, as left axillary and mediastinal lymph node metastases were observed. Exfoliated cells in the pleural effusion were found to be adenocarcinoma cells. In March 2019, immunohistochemistry according to standard procedures [PD-L1 IHC 22C3 pharmDx (ready to use; clone 22C3; cat. no. SK00621; Agilent Technologies, Inc.) incubated at room temperature for 40 min] demonstrated that in the left upper lung mass resection specimen, PD-L1(+) expression in the tumor cells was 10% (Fig. 3). The patient received 6 cycles of chemotherapy (120 mg paclitaxel liposome on days 1 and 7+40 mg cisplatin on days 1-3) plus 100 mg

Table I. Timeline of treatments received by the patient and the subsequent outcome.

Time period	Treatment and dose	Result
October 2017-February 2018	6 cycles; 0.8 g pemetrexed on day 1+0.5 g carboplatin on day 2; every 3 weeks	Progressive disease
March 2019-June 2019	6 cycles; 120 mg paclitaxel liposome on days 1 and 7+40 mg cisplatin on days 1-3+100 mg pembrolizumab on day 4; every 3 weeks	Progressive disease
July 2019-October 2019	5 cycles; 100 mg pembrolizumab on day 1; every 3 weeks	Progressive disease
November 2019-January 2020	4 cycles; 210 mg paclitaxel liposome on day 1+100 mg pabolizumab on day 3; every 3 weeks	Progressive disease
February 2020	1 cycle; 210 mg paclitaxel liposome injection on day 1+400 mg carboplatin on day 1+100 mg pembrolizumab on day 3; every 3 weeks	Progressive disease
February 2020-May 2020	4 cycles; 200 mg albumin-bound paclitaxel on day 1, 100 mg on day 8+240 mg toripalimab on day 2; every 3 weeks	Progressive disease
May 2020-July 2020	3 cycles; 240 mg toripalimab on day 1; every 3 weeks	Progressive disease
July 2020-August 2020	2 cycles; 200 mg albumin-bound paclitaxel on day 1+240 mg toripalimab on day 2; every 3 weeks	Progressive disease
September 2020-September 2023	50 cycles; 12 mg anlotinib on days 1-14+240 mg toripalimab on day 1; every 3 weeks	Stable disease

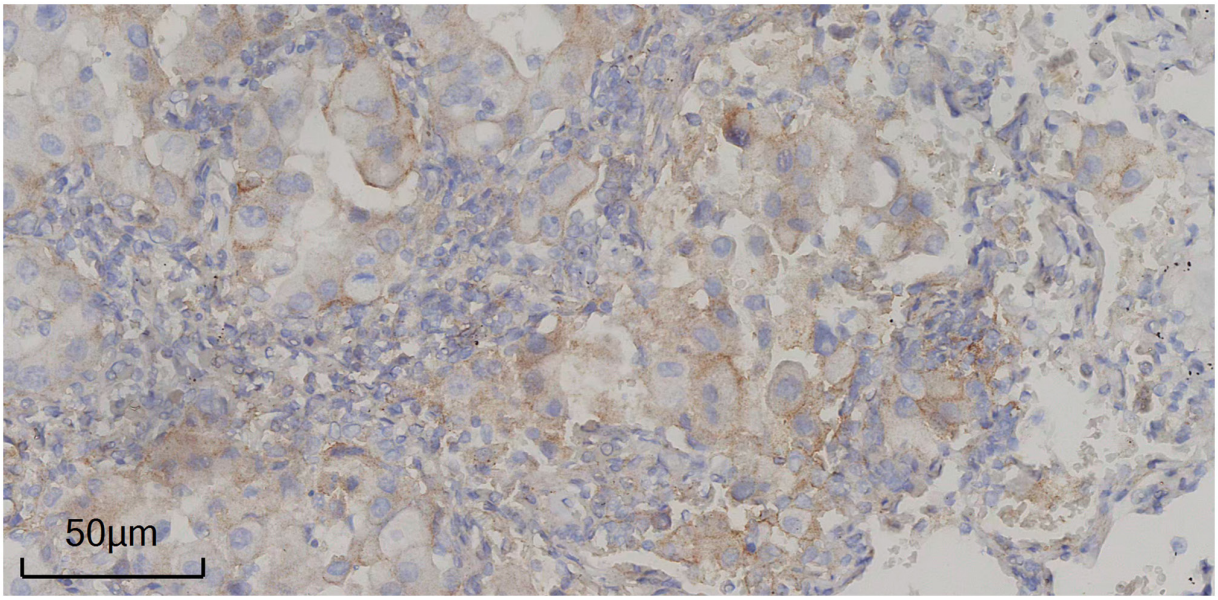

Figure 3. Programmed cell death-ligand 1 expression of the left upper lung mass resection specimen, determined using immunohistochemistry.

pembrolizumab on day 4 from March 2019 to June 2019. After treatment, tumor indicators were all reduced to their normal ranges, including the serum carcinoembryonic antigen (CEA; normal ranges, <5.00 ng/ml), carbohydrate antigen 125 (CA-125; normal ranges, <35.00 U/ml), CA-153 (normal ranges, <31.30 U/ml), serum ferritin (SF; normal ranges, 11.00-306.8 ng/ml) (Fig. 4). The patient received 5 cycles of 100 mg pabolizumab on day 1 from July 2019 to October 2019. However, in November 2019, the serum carcinoembryonic antigen (CEA) level (15.78 ng/ml) was markedly higher once more, indicating tumor progression.

The patient received 4 cycles of chemotherapy (210 mg paclitaxel liposome on day 1+100 mg pembrolizumab on day 3) from November 2019, to January 2020, and then underwent a bone ECT scan in an external hospital due to right hip pain. This demonstrated an abnormal concentrated shadow at the left edge of the right ilium and L5 vertebra, indicating active metabolism. Chest CT demonstrated a small amount of pleural effusion on the left side following left upper lung surgery (a video-assisted left superior lobectomy), similar to that found on the CT scan performed in November 2019, and focal fibrosis of the left lung with pleural thickening and right iliac bone metastasis, with increased progression compared with previous scans from February 2020. A plain MRI scan of the lumbar spine and hip joint demonstrated lumbar degeneration, lumbar 1/2, 2/3, 3/4 and 4/5, and lumbar 5/sacral 1 intervertebral disc protrusion,

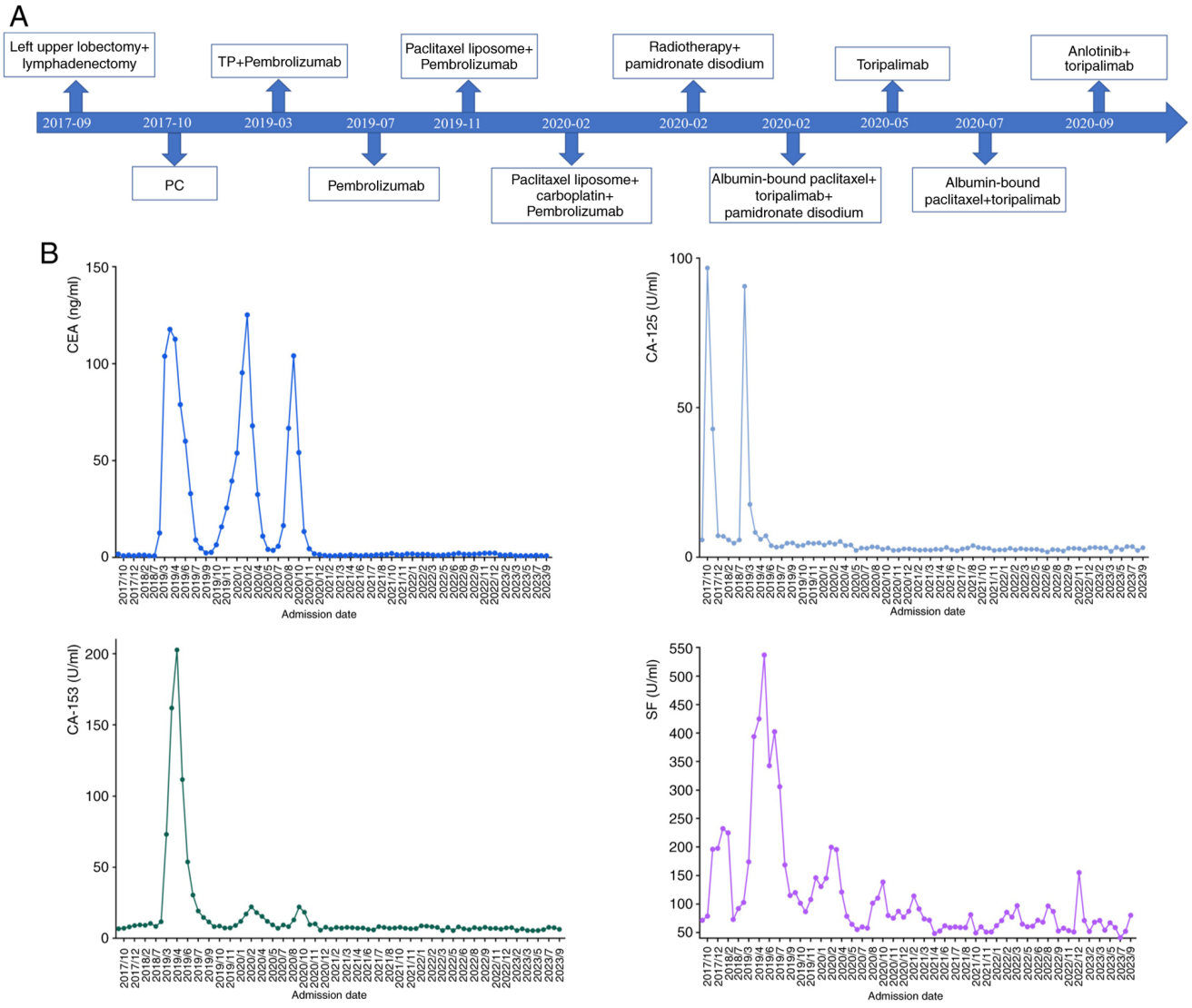

Figure 4. Treatment and serum test results of the patient. (A) Complete treatment plan received by the patient and (B) the tumor indicators over time. PC, pemetrexed + carboplatin; TP, paclitaxel+ cisplatin; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; SF, serum ferritin.

and metastasis of the right iliac wing. In February 2020, the patient was administered 1 cycle of 210 mg paclitaxel liposome and 400 mg carboplatin on day 1, and 100 mg pembrolizumab on day 3. Radiotherapy was indicated in accordance with the Chinese Society of Clinical Oncology guidelines (18), and the patient underwent radiotherapy (range, right iliac bone and surrounding soft tissue; dose, 40 Gy/20 fractions combined with pamidronate disodium for anti-bone metastasis treatment) in February 2020.

In February 2020, CEA (125.19 ng/ml) was notably higher compared with before in February 2020 (CEA, 95.38 ng/ml), indicating the progression of the disease. The patient received 4 cycles of albumin-bound paclitaxel at 200 mg on day 1 and 100 mg on day 8+240 mg toripalimab on day 2 combined with pamidronate disodium for anti-bone metastasis treatment from February 2020, to May 2020. The patient then received immune maintenance therapy (240 mg toripalimab) from May 2020, to July 2020. The lactate dehydrogenase (LDH, normal ranges 135-225 U/l) levels of the patient started to be assessed since June 2020 (Fig. 5). The CEA level (16.44 ng/ml) was markedly higher than that in July 2020. The treatment plan was changed to 200 mg albumin-bound paclitaxel on day 1+240 mg toripalimab on day 2 in July 2020 and the same treatment plan was conducted in August 2020. The patient's tumor indicators continued to increase, suggesting drug resistance. The patient received targeted therapy combined immunotherapy (12 mg anlotinib on days 1-14+240 mg toripalimab on day 1) from September, 2020, to September, 2023.

In November 2022, chest and abdominal CT demonstrated postoperative changes to the left upper lung lobe, including scattered fibrous lesions in the left lung, localized thickening of the left pleura, fine calcification in the right lower lung lobe, calcification in the right lobe of the liver, right iliac bone destruction and multiple high-density shadows of the lumbosacral vertebral body, similar to the findings of the previous CT scan performed in August 2022. In March 2023, and July 2023, chest and abdominal CT demonstrated the same aforementioned features.

At the time of writing the present report (September 2023), the patient had accumulated >36 months of PFS and

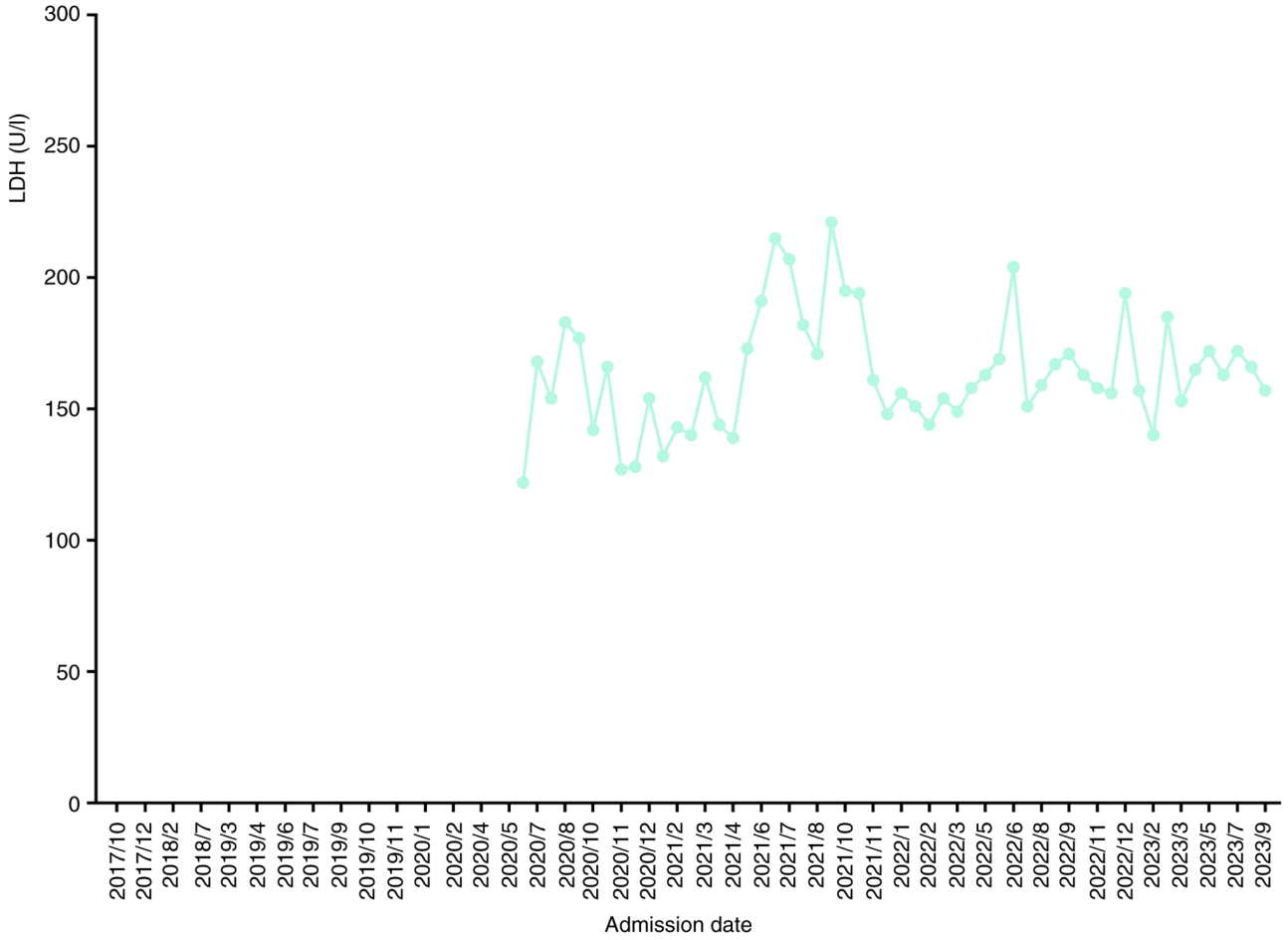

Figure 5. LDH levels since June 2020. LDH, lactate dehydrogenase.

>72 months of OS. The patient's quality of life was good and stable, and activities of daily living were complete without the need for care. Moreover, the patient in the present study continued to receive a traditional Chinese medicine (TCM) treatment in the form of a decoction of Glehnia and Ophiopogon alongside targeted therapy and immunotherapy, in the Department of Oncology.

Discussion

Recurrence and metastasis pose a significant threat to the prognosis of patients with NSCLC (19). Studies have reported that anti-PD-1 immunotherapy exhibits antitumor efficacy in patients with advanced lung cancer (20,21). With advances in Chinese health care reforms, an increasing number of targeted therapies and immunotherapies have been included in medical insurance programs, to benefit an increasing number of patients and reduce the financial burden on individuals.

In the present study, the case of a patient with advanced lung cancer is reported. Systemic therapies, such as chemotherapy and immunotherapy, failed and the patient subsequently received targeted therapy (12 mg anlotinib on days 1-14) and anti-PD-1 immunotherapy (240 mg toripalimab on day 1) when multiple metastases were observed. Long-term survival was achieved, determined based on tumor indicators and CT results. The patient survived for >4 years following lung cancer progression, which is notably longer than expected for patients with advanced lung cancer (median PFS of 4-5 months and OS of 16-18 months) (22). This long-term survival demonstrated the notable potential of targeted therapy and anti-PD-1 immunotherapy for the treatment of advanced lung cancer. However, the present report focused on only one case and therefore there is a lack of high-quality evidence (large sample and randomized); thus, large-scale multi-center randomized controlled trials are required.

A previous case study reported that a patient with advanced NSCLC received multi-line therapy, including chemotherapy combined with targeted therapy (consisting of pemetrexed, carboplatin and bevacizumab), chemotherapy with abraxane, anlotinib targeted therapy and subsequent single-agent treatment with toliximab, with no progression for 13 months (23). Another study reported that a patient with late-stage NSCLC and EGFR-sensitized mutations responded to topolizumab combined with chemotherapy after resistance to osetinib, with a PFS time of >8 months and an OS time of >28 months (24). A multicenter phase II trial involving patients with advanced NSCLC and EGFR mutations who were previously treated with an EGFR-TKI, administered treated with tolipizumab + chemotherapy as a second-line treatment. The study reported a median PFS of 7 months and an OS of 23.5 months (25). A phase III study reported that the combination of toripalimab with first-line chemotherapy for advanced NSCLC significantly improved PFS time compared with placebo combined with

chemotherapy, with a median PFS time of 8.3 months compared with 5.6 months, respectively (26). It is important to follow up on patients to observe the outcomes and prognosis, which can help to improve clinical diagnoses and treatments. Tumor markers, such as CEA, can be used to observe disease progression. However, when assessing progression, LDH should also be assessed, as it is a good indicator of a tumor (27). The Affiliated Hospital of Nanjing University of Chinese Medicine only began to routinely test patients' LDH levels in June 2020; therefore, the patient's LDH levels in the present study were not assessed before June 2020.

Most cancer patients with a Chinese background tend to seek TCM treatment (28), which has been reported to alleviate clinical symptoms, prolong survival time and decrease the adverse effects of conventional therapy (29). The pathogenesis theory of cancerous toxins is a TCM-based theory on the differentiation and treatment of tumors (30). Studies have reported that TCM decoctions, such as the Long-Zhua-Jie-Du decoction based on the pathogenesis theory of cancerous toxins, may have anticancer effects on advanced lung cancer (31). Tumorigenesis is a multistep process, and its occurrence and developmental mechanisms remain to be fully explored. In a case where single therapy may have little or no effect, holistic integrative medicine may be utilized (32). Furthermore, a combination of multiple therapies, including conventional therapy, targeted therapy, immunotherapy, and complementary and alternative medicines, such as TCM (33), are a relatively newer route for the treatment of tumor and metastasis in the last 5 years. Research has showed that Qianjinweijing decoction combined with chemotherapy improves the quality of life of patients, and prolongs the survival time of patients with advanced NSCLC (34).

In conclusion, the present patient survived for >4 years following lung cancer progression, which is notably longer than expected for patients with advanced lung cancer. The present case demonstrated the efficacy of targeted therapy and anti-PD-1 immunotherapy for the treatment of advanced lung cancer following the occurrence of drug resistance and progressive disease.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TG and HC made substantial contributions to the conception and design of the study. TG, WZ and SZ were primarily responsible for writing the manuscript. TG, WZ, SZ, WQ, YW, XL and FK were responsible for collecting the patient's clinical data and data analysis. TG and HC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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