

Case Report

A Rare Case of Complete-Immunotherapy-Responsive Metastatic Non-Small Cell Lung Cancer with Long Lasting Progression-Free Survival: A Case Report

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Abstract: Background and introduction: Lung cancer is a prevalent and deadly disease globally. Non-small cell lung cancer (NSCLC) is the most common subtype, comprising 85% of cases. Case report: A 65-year-old male ex-smoker presented to our facility with a nocturnal cough. Various investigations revealed that he had metastatic NSCLC, for which he underwent chemotherapy with cisplatin and gemcitabine, followed by immunotherapy with Nivolumab. He achieved a complete response to the therapy and has remained free from recurrence for over 7 years since the initial diagnosis. Discussion and Conclusions: The treatment of metastatic NSCLC remains a significant therapeutic challenge, but the implementation of new therapeutic techniques has expanded the possibilities of achieving complete and durable eradication of the disease.

Keywords: NSCLC; metastasis; immunotherapy; complete response; case report; literature review



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1. Introduction

Lung cancer is the second most prevalent neoplastic disease globally, with 2,206,771 new cases in 2020 (11.4% of all new cancer diagnoses), and is the leading cause of cancer-related deaths, with 1,796,144 deaths in 2020 (18% of all cancer deaths) [1]. It predominantly affects males [2], and tobacco smoking is the primary etiological factor [3], with the incidence correlated with smoking prevalence in different countries [4]. Other contributing factors include exposure to radon [5], a history of chronic obstructive pulmonary disease (COPD), interstitial lung diseases [6], and the consumption of red meat [7]. Non-small cell lung cancer (NSCLC), comprising adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, is the most common histological subtype, constituting 85% of cases [8]. NSCLC is often diagnosed at the onset of more advanced symptoms such as the presence of hemoptysis, chest pain, and dyspnea [9].

This study presents a case of metastatic NSCLC achieving complete remission (CR) and extremely long progression-free survival (PFS) through immunotherapy.

2. Case Report

A 63-year-old male patient presented at our hospital in 2016 with a worsening non-productive night cough but no dyspnea. He had a history of hypertension and a recent

diagnosis of gastroesophageal reflux. A former smoker who quit 10 years ago, he had not experienced weight loss in recent months. An abdominal ultrasound revealed an area near the hepatic hilum with lobulated contours, roughly oval, displaying an iso-hypoechoic structure, with a maximum diameter of 43 mm, indicating the presence of malignant lymph nodes (Figure 1a–c).

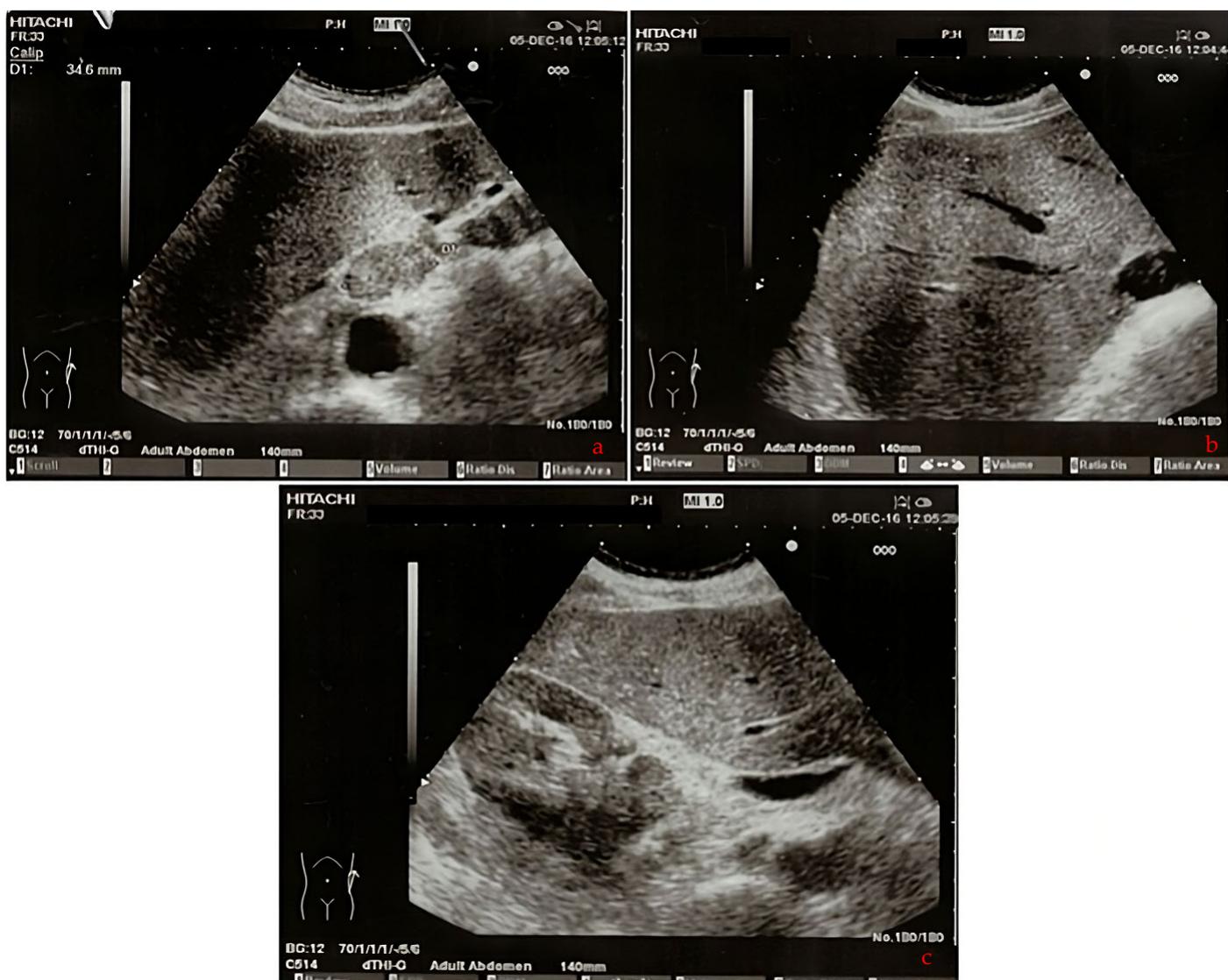


Figure 1. (a–c) The abdomen ultrasound images of perihepatic lymphadenopathy (2016).

A total-body CT (computed tomography) scan was performed, which confirmed this suspicion and revealed the presence of a solid, nodular-like, expansive process in the right upper lobe of the lung (21 × 29 mm, adjacent to the subclavian artery) and multiple lymphadenopathies in the mediastinum (paratracheal and subcarinal) and abdomen (near the origin of the celiac trunk and periaortic lymph nodes) (Figure 2).

Bronchoscopy and cytology of bronchial lavage returned negative results, while FDG PET (fluorodeoxyglucose positron emission tomography) confirmed the presence of multiple hypercapturing lesions consistent with the CT findings. Subsequently, an ultrasound-guided biopsy was performed on lymph nodes near the celiac tripod (Figure 3).

A histological examination described a poorly differentiated neoplasm suggestive of primary lung cancer. Immunohistochemistry results were positive for CKAE1/AE3, CK7, EMA, and focally for TTF1 and p63, while negative for CK5/6, CD56, Chromogranin A,

and Synaptophysin. The Ki67 value was 50%. The study on EGFR for the mutation of exons 18, 19, 20, and 21 gave a negative result.

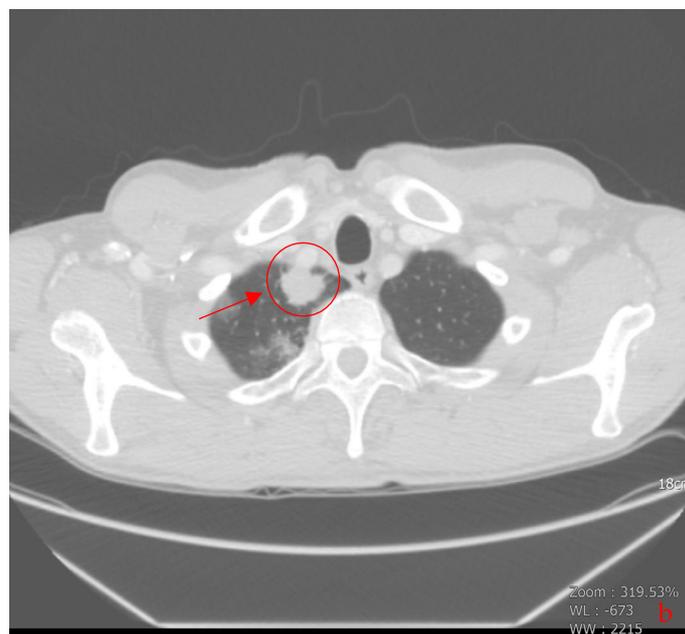


Figure 2. (a,b) The axial CT scan revealed a solid, nodular-like, expansive process in the right upper lobe of the lung (marked with a red circle) (a). To the right: lung windowing (b) (2016).

Various tumor markers were measured, indicating a primary non-small cell lung carcinoma (NSCLC): CEA was 1021.2 ng/mL (<6), Ca 19.9 was 9.0 UI/mL (<37), and NSE was 6.6 UI/mL (<10).

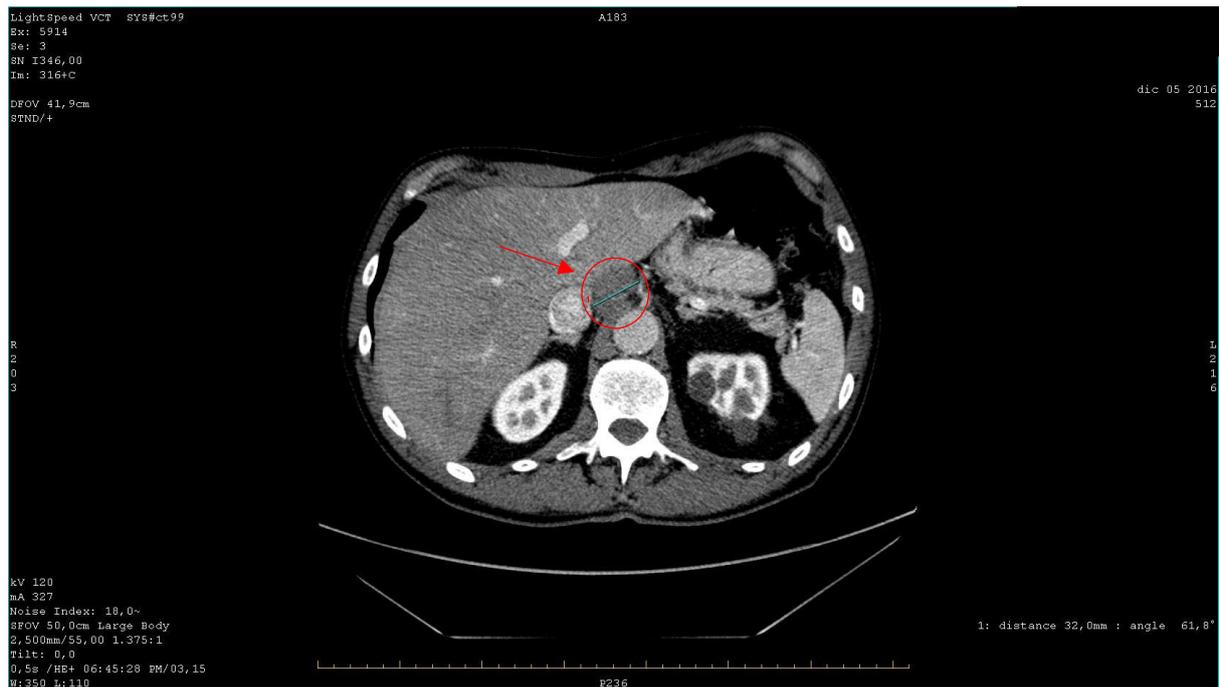


Figure 3. The axial CT scan of abdomen with contrast medium shows tripod lymphadenopathy (marked with a red circle) (2016).

Given the metastatic stage of the disease, surgical removal of the primary lesion was not pursued. The patient started a chemotherapy regimen consisting of cisplatin (70 mg/m² on day 1 every 21 days) and gemcitabine (1000 mg/m² on days 1 and 8 every 21 days) [10,11]. After three cycles, blood tests showed hyponatremia (Na⁺ 127 mEq/mL, successfully treated) and a favorable response in cancer markers: CEA decreased from 1021.2 ng/mL to 116.2 ng/mL, and Ca15.3 decreased to 27.5 UI/mL (<30 UI/mL). Subsequent CT scans revealed a partial response to therapy with a reduction in the size of the lung tumor (from 21 × 29 mm to 10 × 15 mm) as well as thoracic and abdominal lymphadenopathies. Three additional cycles were planned, but the patient could only complete two cycles due to bone marrow suppression and subsequent anemia, which required two blood transfusions. The patient underwent bone scintigraphy, which yielded negative results for metastases in the skeletal system. Following another CT scan, which showed progression of the disease in the subdiaphragmatic lymph nodes, the patient started immunotherapy with Nivolumab (3 mg/kg every two weeks) (PD-L1 expression < 10%).

This treatment showed a positive response with a progressive decrease in CEA levels (reaching 3 ng/mL after six months) and Ca 15.3 (22, ng/mL) and a reduction in the size of the lesions observed in subsequent CT scans (no new lymphadenopathies and a reduction in existing ones). After 18 months, Nivolumab was discontinued, as agreed with the patient, considering his positive response to therapy and the elevated risk of potential adverse reactions, compounded by his related apprehension. The patient developed pruritus unresponsive to antihistamines, which was managed with glucocorticoids. Over the next 3 years, regular monitoring with CEA, Ca15.3, and CT-PET scans indicated a complete response. CEA levels remained stable below 6 ng/mL, and subsequent CT-PET scans revealed the absence of areas exhibiting FDG uptake in the thoracic and abdominal regions. In the latest total body CT scan performed in 2023, no evidence of neoplastic disease was detected in the lung parenchyma or in the subdiaphragmatic, paratracheal, subcarinal, or periceliac lymph nodes (Figure 4). The complete timeline of the case is reported in Table 1.

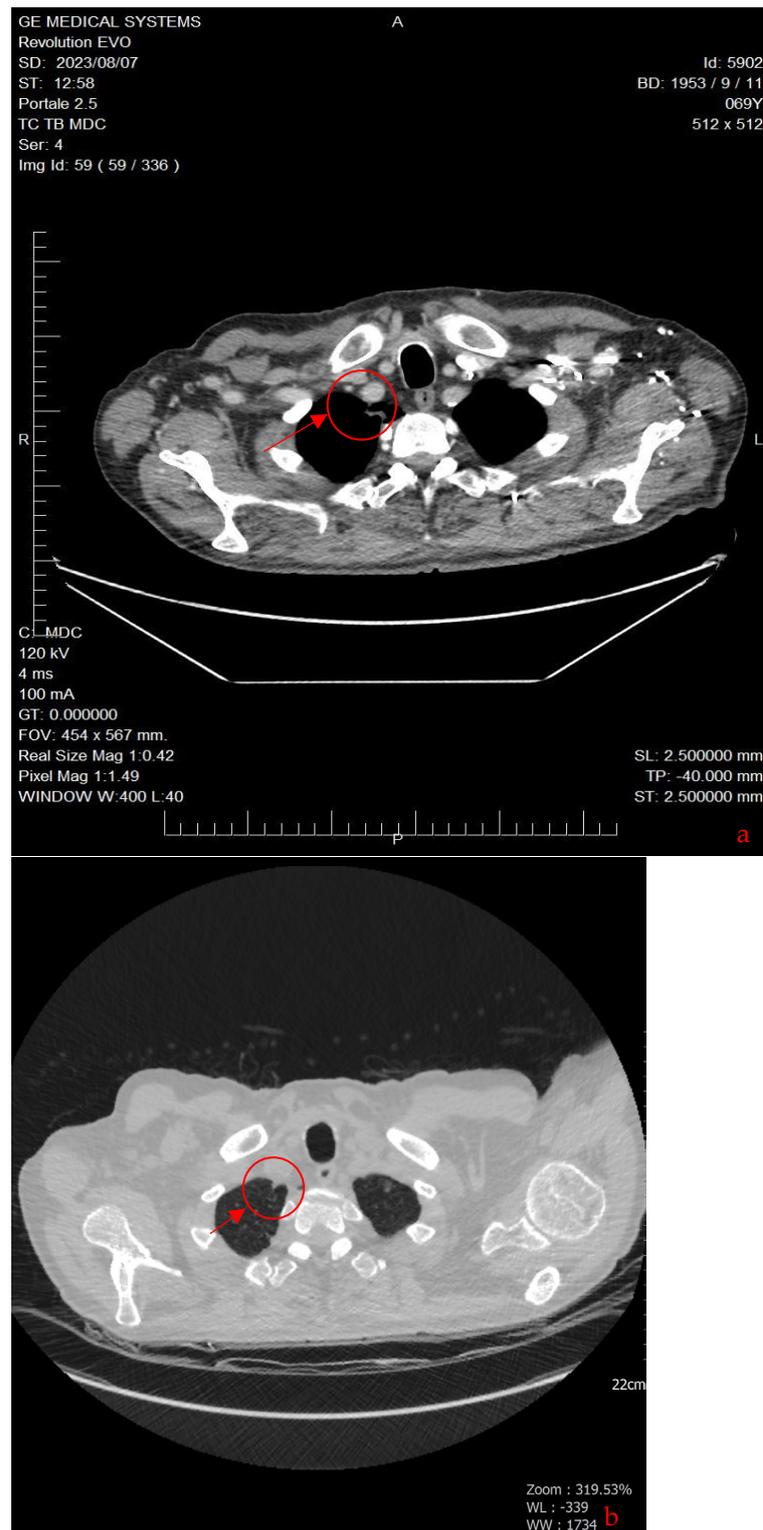


Figure 4. The axial CT scan shows that the solid, nodular-type, expansive process in the right upper lobe of the lung is no longer visible (red circle). This means that the nodule has disappeared or shrunk to a size that is no longer detectable on the CT scan (a). To the right: lung windowing (b) (2023).

Table 1. Timeline and relevant data.

| Year | Event | Relevant Data |
|------|---|--|
| 2016 | Patient presentation Diagnosis Abdominal ultrasound Total body CT scan | Worsening non-productive night cough, no dyspnea. Metastatic lung cancer. Presence of malignant lymph nodes near the hepatic hilum. Solid nodular- like expansive process in the right upper lobe of the lung and multiple lymphadenopathies in the mediastinum and abdomen. |
| 2016 | US-guided biopsy Immunochemistry EGFR mutation study | Poorly differentiated neoplasm suggestive of primary lung cancer. Positive for CKAE1/AE3, CK7, EMA, focally for TTF1 and p63. Negative for CK5/6, CD56, Chromogranin A, and Synaptophysin. Ki67 value: 50%. Negative result for exons 18, 19, 20, and 21. |
| 2016 | Chemotherapy initiation | Cisplatin (70 mg/m ² dL every 21 days) and gemcitabine (1000 mg/m ² , d 1, 8 every 21 days). |
| 2016 | Partial response to therapy | Reduction in the size of the lung tumor and lymphadenopathies. |
| 2017 | Bone scintigraphy | Negative results for skeletal metastases. |
| 2017 | Immunotherapy initiation | Nivolumab (3 mg/kg every two weeks). |
| 2019 | Nivolumab discontinuation | Complete response observed. |
| 2023 | Latest total body CT scan | No evidence of neoplastic disease detected. |

3. Discussion and Conclusions

The patient in our case study presented with nonspecific symptoms, a history of heavy smoking (although currently not a smoker), and no previous access to cancer screening programs. The diagnosis of cancer was therefore incidental, although already at an advanced stage (T1c-N3-M1c Stage IV B according to the eighth edition of the AJCC TNM classification [12]).

It is quite common for many patients with NSCLC to be diagnosed with symptomatic disease or even at the metastatic stage (37.9%) [13]. However, this poses a problem because several studies have shown that in patients with a heavy smoking history, participation in screening programs (typically performed using low-dose CT techniques [14]) significantly reduces mortality from this condition through early detection [15,16]. Despite this, only about 4% of high-risk patients (people with a ≥ 20 pack-year smoking history, those who currently smoke, those who have quit within the past 15 years, and those who are between 50 and 80 years old [17]) participate in screening programs [18].

During the case management, we found that CEA (carcinoembryonic antigen) was a reliable predictor of disease progression and regression, consistent with other studies [19].

Given the absence of suitable mutations for targeted therapy, the initial line of treatment was chemotherapy with cisplatin and gemcitabine, as recommended by guidelines at the time [11]. However, this treatment regimen resulted in toxicity, including bone marrow depression, leading to the need for two blood transfusions, as well as severe hyponatremia. Despite an initial partial response, the disease progressed after treatment suspension due to the mentioned side effects.

Subsequently, the patient started immunotherapy with Nivolumab at a dose of 3 mg/kg every 3 weeks. This led to a complete response, and the patient has remained disease-free since the treatment was discontinued in mid-2018, which is now five years ago. Over time, immunotherapy has demonstrated good efficacy in the treatment of metastatic NSCLC, as supported by another works [20]. A potential concern in patient management may arise following the cessation of immunotherapy. However, our observations did not indicate any relapse or recurrence of the disease. This aligns with subsequent studies that demonstrated no declines in progression-free survival (PFS) or overall survival (OS) among oncological patients who had to discontinue Nivolumab-based immunotherapy due to adverse effects [21,22].

An apical resection of the right upper lobe was not executed for two primary reasons: Firstly, the patient was diagnosed with Stage IV disease, making surgery inconsistent

with the guidelines applicable during the treatment period. Secondly, the patient declined surgical intervention [11].

It is important to state that cases like this, with patients experiencing a complete response to treatment and maintaining a disease-free state for over 5 years, are still not common in the context of NSCLC, and only anecdotally reported in the literature. Despite ongoing advancements in research and the increasingly detailed molecular characterization, tumor-related mortality and the rates of overall survival (OS), recurrence-free survival (RFS), and progression-free survival remain suboptimal [23].

Indeed, achieving such extended overall survival (OS) times (at the time of writing the article, 75 months, calculated from the date of diagnosis of the disease) in a patient with Stage IVB non-small cell lung cancer (NSCLC) and negative for EGFR/ALK mutations who could not undergo radical tumor resection is exceedingly rare. A retrospective Austrian study conducted in 2015 [13], which examined 2993 patients treated between 1989 and 2009, reported a median OS of 7.2 months for patients treated prior to 2000 and 8.4 months for patients treated after 2000, considering recurrence-free survival (RFS) for patients receiving chemotherapy (up to five different therapeutic regimens) in this patient cohort. A recent American article that considered various treatment options with chemotherapy (carboplatin in combination with paclitaxel or pemetrexed) reported similar overall survival (OS) data, with a median OS of 6.8 months for patients treated with first-line chemotherapy [24].

Higher values have been achieved with the use of immunotherapy. In the KEYNOTE-024 trial, the use of Pembrolizumab was evaluated in patients with Stage IV NSCLC and a PD-L1 tumor proportion score of 50% or greater, without EGFR/ALK mutations. In this patient pool, the median OS was reported to be 30 months [25,26].

Other trials have evaluated the response to immunotherapy with Pembrolizumab in combination with Carboplatin and Paclitaxel chemotherapy in patients with non-small cell squamous carcinoma, regardless of PD-L1 expression. These trials reported a median OS of 15.9 months in patients treated with the combination compared to 11.3 months in patients treated with chemotherapy alone. The hazard ratio for death was 0.64 in patients with a PD-L1 expression greater than 50%, 0.57 in patients with a PD-L1 expression between 1% and 49%, and 0.61 in patients with a PD-L1 expression less than 1% [27].

Similar results were also obtained in the KEYNOTE-042 trial. In this trial, the response to Pembrolizumab monotherapy was evaluated in patients with non-small cell lung cancer, regardless of PD-L1 expression. The trial demonstrated a comparable median overall survival (OS) of 16.7 months in patients treated with Pembrolizumab compared to 12.1 months in patients treated with standard chemotherapy [28,29].

Other studies have evaluated the combination of immunotherapy with stereotactic body radiation. In a 2020 study, the response was assessed in patients with metastatic NSCLC using either Pembrolizumab or Ipilimumab (anti-CTLA-4) combined with radiation treatment of 50 Gy at the site of the primary lesion. The median overall survival (OS) of patients treated with Ipilimumab was reported to be 10.7 months, while it was not determined during the study of patients treated with Pembrolizumab (with a survival rate of 66% at 18 months). These findings suggest that combining immunotherapy with stereotactic body radiation may provide favorable outcomes for patients with metastatic NSCLC [30].

In the literature, cases with an overall survival (OS) exceeding 36 months are rare. A Chinese case report from 2021 [31] described a 78-year-old male patient with a history of prolonged tobacco abuse (20 cigarettes per day) and tuberculosis, diagnosed with NSCLC Stage T1N0M0, who underwent surgery and radiation therapy. After one year of radiation treatment, the patient developed lung, liver, cardiac, and bone metastases. Subsequently, the patient received radiation therapy for the bone lesions and was administered pembrolizumab (200 mg every 21 days). The patient showed symptomatic improvement with a partial response (PR) as evidenced by CT scans. The authors reported a 7-year overall survival (OS) from the time of diagnosis, similar to the presented case, with the difference

being that the patient developed metastases 3 years after the initial diagnosis, rather than at the time of initial diagnosis.

Another similar case was reported in a French study from 2022 [32], describing a 61-year-old female patient (with a heavy smoking history) with non-small cell lung cancer (NSCLC) and bone, liver, and adrenal gland metastases. Molecular screening with next-generation sequencing (NGS) of the primary lesion identified EGFR mutations (V843I, a mutation not associated with a treatment benefit from targeted therapy) and KRAS G13D. Subsequently, the patient received systemic treatment with Pembrolizumab (PD-L1 > 50%), resulting in a partial response in all tumor locations. After 30 months of progression-free survival (PFS), the patient experienced progression at the previous metastatic sites and underwent chemotherapy with pemetrexed and carboplatin, with a reported overall survival (OS) of 48 months.

Another Chinese study published in 2023 [33] reported a partial response duration of 45 months in a 66-year-old male patient undergoing systemic therapy with pembrolizumab (200 mg every 21 days). The management of the patient was challenging due to the presence of chronic renal insufficiency and the absence of immune-related adverse events (irAEs).

Another exceptional case of overall survival (OS) was described in a 2019 Japanese article [34], involving a 71-year-old male patient diagnosed with lung adenocarcinoma. Initially, the patient underwent chemotherapy with carboplatin and docetaxel, achieving a partial response that lasted for 8 months. However, the disease eventually progressed, leading to repeated cycles of re-challenging chemotherapy, which successfully controlled the disease for 6 years. Subsequently, the patient received treatment with erlotinib, resulting in a partial response. With a survival time exceeding 11 years from the time of diagnosis, this case is noteworthy. However, it differs from the case previously reported as it lacks a complete response to therapy.

A similar story is that of a 73-year-old American patient [35] who underwent immunotherapy with Nivolumab and achieved a survival time of approximately five years from the time of diagnosis. However, it should be noted that there was no complete response to the treatment.

Lastly, another noteworthy case is that reported in a 2020 Chinese study [36] of a patient with NSCLC and brain metastases who was treated with Temozolomide (150 mg/m²/d for 5 days every 28-day cycle) and achieved an overall survival (OS) of 55 months.

It still remains problematic to identify the reasons for this exceptional survival, firstly precisely because of the rarity of the case, which prevents us from having a sufficiently large population to study, and secondly because of the lack of sufficiently accurate data on specific patient characteristics.

It is evident that long-term survival for patients with metastatic NSCLC remains short despite the use of increasingly advanced medical and pharmaceutical technologies. In this scenario, the collection and study of exceptional patients and cases (and also studying the immunological characteristics of these patients) with long-term survival become increasingly crucial in the search for better treatment options for this patient population.

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