CASE REPORT

Long-Term Response to PD-1 and CTLA-4 Blockade in an SCLC Patient with Negative PD-L1 Expression on Biopsy: A Case Report

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ABSTRACT

Despite recent advances in the availability of new therapeutic agents, small-cell lung cancer (SCLC) remains an aggressive disease with a poor prognosis. While immune checkpoint inhibition has revolutionized the treatment of non-small cell histologies, results in SCLC have shown overall less favorable evolution, and despite initial data from different trials showing potential for development, the lack of reliable biomarkers for patient selection is a major hindrance to their use. Most notably, programmed death-ligand 1 (PD-L1) expression does not appear to play a key role in SCLC responsiveness to immune checkpoint inhibition. While other biomarkers such as tumor mutational burden (TMB) have been suggested to be more relevant, literature data are not univocal on this subject.

We report here on a 58-year-old patient with metastatic PD-L1-negative SCLC treated in an advanced and symptomatic setting who obtained a complete and sustained clinical and radiological response to the combination of nivolumab and ipilimumab. We also discuss the impact of treatment-related adverse events, such as autoimmune hypothyroidism, gastroenteric toxicity and pneumonitis, on his quality of life. This case, while it exemplifies the potential of immune checkpoint inhibition in SCLC, highlights the need for a deeper understanding of the mechanisms underlying its efficacy in order to identify patients who are more likely to benefit from treatment.

Keywords: *small-cell lung cancer, immune checkpoint inhibition, PD-1, CTLA-4*

INTRODUCTION

The therapeutic relevance of immune checkpoint inhibitors in small-cell lung cancer (SCLC) has generally proven inferior to that in non-small cell histotypes, and biomarkers for patient selection are lacking. We report on a patient with SCLC showing prolonged response to combined programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) targeting.

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CASE REPORT

Our 58-year-old male patient had a history of chronic non-obstructive pulmonary disease and cerebellar ischemic ictus in 2013; he was an active smoker (80 pack/year) until December 2016. Due to malaise and postural instability, he underwent a brain computed tomography (CT) scan and magnetic resonance imaging (MRI) which showed multiple sub- and supratentorial lesions. A positron emission tomography (PET)/CT scan detected mediastinal lymphadenopathies, skeletal localizations and an apical nodule in the right lung.

An endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was carried out and led to a cytological diagnosis of SCLC located in the mediastinal lymph node stations 4R and 2R. The patient was therefore started on first-line palliative chemotherapy with four cycles of carboplatin and etoposide, in addition to panencephalic radiotherapy. Re-evaluation in March 2017 showed partial disease response and consolidation radiotherapy was administered on the most F-fluorodeoxyglucose (FDG)-active sites (mediastinum and left scapula). A new PET/CT scan in August 2017 showed mediastinal and adrenal disease progression. A re-challenge with four cycles of carboplatin and etoposide was proposed and successfully carried out between September and November 2017, and re-evaluation imaging showed a mixed response to the treatment. Again, radiotherapy was administered on the most active localizations of the disease (pre-tracheal and adrenal).

Over the following months, the disease showed minimal radiological progression that did not require immediate treatment. In August 2018, a PET/CT scan detected significant progression and a second re-challenge with carboplatin and etoposide was started but had to be interrupted due to a severe allergic reaction at the start of the second cycle. The patient refused further chemotherapeutic treatment with topotecan.

A biopsy sample was obtained in order to evaluate programmed death-ligand 1 (PD-L1) expression. The biopsy was performed on a sample of soft tissue from the area that was later treated with radiotherapy and showed 0% PD-L1 expression. A new PET/CT scan was performed in October 2018, demonstrating further disease progression; the patient was symptomatic and his general condition was in decline. Considering his refusal to undergo further chemotherapy, we explored other available treatment options.

At the time, an analysis of initial data from the CheckMate 032 study performed by Hellmann et al. (2018) had shown promising results with nivolumab plus ipilimumab in patients with advanced SCLC progressing on platinum-containing therapy and a high tumor mutational burden (TMB), with a 1-year overall survival (OS) rate of 62%.[1] Patients with low or medium TMB treated with either nivolumab plus ipilimumab or nivolumab alone had a 1-year OS rate of 20–26%, which is still a clinically significant result in this setting. PD-L1 positivity did not appear to be predictive of response.

Based on these data, the patient started the treatment with nivolumab plus ipilimumab with a personalized schedule (nivolumab 3 mg/kg every three weeks; ipilimumab 1 mg/kg every six weeks). Clinical benefit was rapidly evident and a PET/CT scan performed in December 2018 showed partial disease response, with a collateral appearance of thyroid uptake that was attributed to autoimmune thyroiditis (**Figure 1**). A further re-evaluation with PET/CT scan and brain MRI in February/March 2019 showed near complete response. The clinical benefit was maintained; however, the patient developed severe symptomatic hypothyroidism that was successfully managed with hormone supplementation.

In June 2019, the patient began to complain of diarrhea that had appeared approximately one month earlier. Autoimmune colitis secondary to the ongoing treatment was suspected, but no specific investigations were made due to the mildness of the symptom which did not significantly interfere with the patient's daily activities and well-being. Symptomatic management with antidiarrheals was attempted without significant changes in stool frequency, and the combination immunotherapy was continued until July 2019, when a total of 7 doses of ipilimumab and 13 doses of nivolumab had been administered. Between July and August 2019, the persistence and worsening of diarrhea required treatment suspension. The patient was started on mesalazine, which led to an initial improvement in symptoms. However, by the end of August 2019, the patient's general condition worsened, with the appearance of symptoms suggestive of an upper gastroenteric disorder: nausea, vomiting, lack of appetite, alterations in taste, sarcophobia and epigastric pain. Diarrhea briefly improved and then worsened again.

An upper endoscopy was performed in the first half of September 2019, showing moderate erosive duodenitis and mild gastritis; biopsies were negative for *Helicobacter pylori*. The patient was already receiving proton pump inhibitors, which were increased to 40 mg per day of pantoprazole, and budesonide was introduced at a dose of 9 mg per day. Improvement was swift, with complete resolution of diarrhea and upper digestive symptoms within four to five days; this benefit was maintained when the budesonide dose was decreased to 6 mg per day.

In October 2019, the patient was able to resume immunotherapy with single-agent nivolumab. Budesonide therapy was subsequently reduced to 3 mg per day and then stopped, without recrudescence of diarrhea.

Disease re-evaluation was performed in November 2019 by PET/CT which showed no significant changes, except for suspected pulmonary fibrosis compatible with organizing pneumonia. Brain MRI was repeated in December 2019 due to

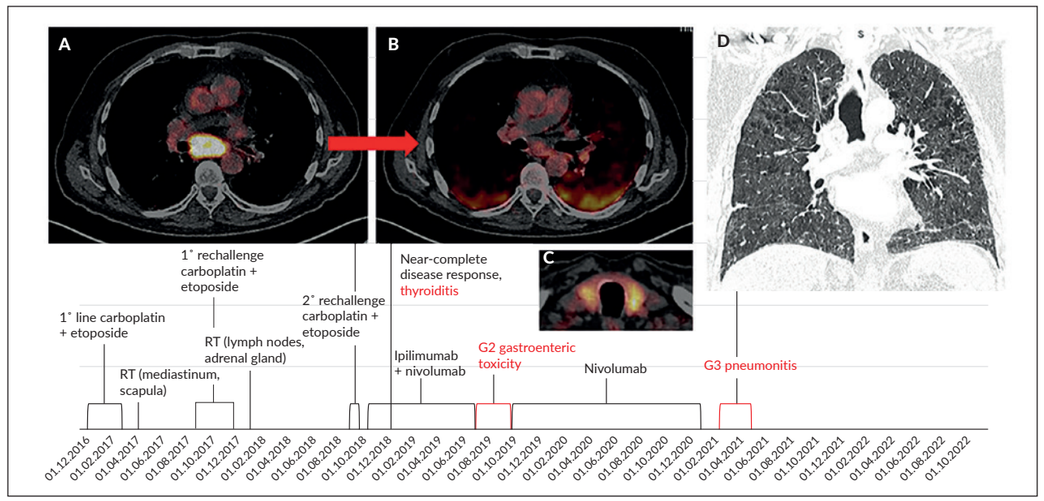

Figure 1. Timeline of events: evolution of positron emission tomography (PET)/computed tomography (CT) images from October 2018 (A) to December 2018 (B and C); pneumonitis as detected by thorax CT scan in March 2021 (D). G2/G3: grade 2/grade 3 according to Common Terminology Criteria for Adverse Events (CTCAE). RT, radiotherapy.

subjective worsening of balance impairment, and detected two small areas of enhancement, which regressed at subsequent follow-up examinations. The next disease re-evaluation was performed in September 2020 and confirmed sustained disease response. A pneumology consultation with an evaluation of lung function was carried out and identified a significantly decreased diffusing capacity for carbon monoxide (DLCO) at 46%, without signs of progressive lung fibrosis requiring treatment.

Treatment with single-agent nivolumab was continued, in the absence of any respiratory symptoms. From March 2020 until the beginning of January 2021, the schedule was modified to a flat dose of 480 mg every four weeks, due to the ongoing SARS-CoV-2 pandemic, to comply with institutional recommendations to reduce the frequency of visits to healthcare structures.

A disease re-evaluation was performed in January 2021 using brain MRI and PET/CT. The PET/CT scan identified two metabolically active, cavitated lesions in the upper right lobe, with satellite lymph nodes. A differential diagnosis was proposed between fungal infection and disease relapse; therefore, bronchoscopy with bronchoalveolar lavage and biopsy was carried out. Pathology results were oncologically negative and microbiology tests detected *Pseudomonas aeruginosa*. The patient who had remained paucisymptomatic until immediately after the diagnostic procedure began manifesting progressively worsening dyspnea, tiredness and reduced oxygen saturation (90–95% at rest).

Antibiotic treatment was started with cefepime due to an anamnestic allergy to penicillin and tendon rupture with quinolones. After the initial benefit, the worsening trend continued, with constant hypotension, severe fatigue and an overall decline in his performance status. The patient refused emergency room access and was managed in an outpatient setting. The COVID-19 test was negative. A contrast-enhanced CT scan of the thorax ruled out embolism and only detected small, peripheral ground glass areas at the upper lobes.

A cardiac cause for dyspnea was excluded by means of normal troponin and pro-B-type natriuretic peptide (proBNP) values, electrocardiogram (ECG) and echocardiography. Peripheral oxygen saturation further worsened over the following day (83–88%), with cyanosis and class 3–4 dyspnea according to the New York Heart Association (NYHA) classification. Lung function tests showed a mild restrictive syndrome and a severe decrease in DLCO (19%).

The patient was empirically started on an intermediate dose of prednisone (0.5 mg/kg) based on the hypothesis of autoimmune pneumonitis, and symptoms showed a slight improvement over the following three days. Considering these results, the prednisone dose was increased to 1 mg/kg with subsequent gradual de-escalation over the course of three and a half months.

Clinical response was rapidly evident, with both subjective improvement in dyspnea and normalization of oxygen saturation and blood pressure. Radiological findings also evolved favorably (**Figure 2**). Lung function tests showed resolution of the restrictive syndrome and improvement of DLCO to 30%. Adverse effects of the treatment included severe irritability that led to a temporary reduction in family contact, insomnia, capillary fragility and peripheral edema. These all gradually receded with prednisone dose reduction until suspension at the beginning of July 2021.

In the context of the SARS-CoV-2 pandemic, the patient received an mRNA-based COVID-19 vaccine as soon as the prednisone dose was below 20 mg/day. After a collegial discussion, it was concluded that the risk associated with severe COVID-19 in a patient with an already precarious pulmonary situation outweighed the risk of adverse reactions or inefficacy due to the ongoing steroid treatment.

A brain MRI was repeated in April 2021 and a PET/CT re-evaluation was performed in May 2021, both showing no evidence of disease. The PET/CT also confirmed regression of the previously identified cavitated lesions and lymph nodes. Treatment with single-agent nivolumab was not restarted due to potential severe toxicity, as the patient was averse to hospital admission. Subsequent PET/CT and MRI examinations confirmed no evidence of disease until July 2022, when a brain MRI detected the appearance of an isolated 2 mm lesion in the left temporal lobe. The finding was re-evaluated at two and five months and showed minimal growth. A new MRI examination is planned in three months, with an option of stereotactic radiotherapy in case of further dimensional increase.

Concerning the quality of life, besides the described events, the patient's main complaints were a lack of lower limb strength and balance impairment, attributable to loss of general condition and previous treatments, alongside impotence

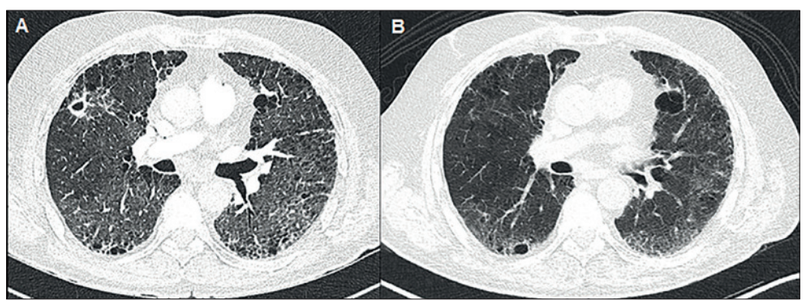

Figure 2. Thorax CT scan in March 2021 (A) and May 2021 (B).

and loss of libido, which were investigated to exclude autoimmune endocrinopathy. No alterations were detected in testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Slightly increased levels of prolactin (411 mU/l, just above the upper limit of normality of 324 mU/l) and accompanying gynecomastia were observed. In light of the patient's apparent predisposition to immune-mediated adverse events, these findings were investigated with a brain MRI, which did not identify signs compatible with autoimmune hypophysitis. The slight increase in prolactin and gynecomastia were therefore attributed to proton pump inhibitor use.

The patient was leading an active life before the COVID-19 pandemic and has been able to resume traveling for pleasure. He also underwent surgical correction of an umbilical hernia as well as minor cosmetic surgery, and his subjective outlook is positive. He is benefitting from physiotherapy with a subjective improvement of his balance and lower limb strength.

DISCUSSION

Longer-term data from the CheckMate 032 randomized expansion SCLC cohort, which tested nivolumab 3 mg/kg every 2 weeks versus nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every three weeks for four cycles, followed by nivolumab 3 mg/kg every two weeks, reported objective response rates of 11.6% in the monotherapy arm and 21.9% in the combination arm, with a median duration of response of 15.8 versus 10 months, respectively.[2] This difference did not translate into a survival benefit, with a median OS of 5.7 versus 4.7 months, respectively, likely due to more adverse events and treatment discontinuation in the combination group. However, the 12-month OS rate was ~30% and the 24-month OS rate was ~18% in both arms, representing a meaningful result in this clinical setting.

Data from this cohort did not confirm an accurate biomarker for predicting the likelihood of response to either single-agent nivolumab or nivolumab plus ipilimumab.[2] TMB did not emerge as a discriminant factor in post hoc analyses and PD-L1 was not evaluated as a biomarker due to the low frequency of PD-L1 expression in the study (12%).

Similarly, the study provided no clear indication concerning the preferable immunotherapy schedule.[2] Our decision to start the patient on a personalized schedule was motivated by clinical need; the choice of dosage and treatment duration was based on expected and observed tolerance. TMB evaluation was not performed beforehand because the patient was symptomatic; moreover, pathology samples had been exhausted and the analysis would have required a new biopsy.

The efficacy of immunotherapeutics in the setting of advanced SCLC has been the subject of further investigation, with the IMpower133 trial showing an OS benefit with first-line carboplatin and etoposide plus atezolizumab versus carboplatin and etoposide plus placebo.[3] No biomarker, including TMB, was identified as predictive of response. Similarly, the CASPIAN trial demonstrated an OS benefit with the addition of durvalumab to first-line platinum and etoposide, although no further benefit was garnered by the addition of tremelimumab.[4]

It should be noted that the clinical course of our patient's disease appeared more favorable than might have been expected of metastatic SCLC with symptomatic brain involvement, even in the setting of the initial treatment with chemotherapy and radiotherapy, which - overall - maintained clinical disease control for almost two years. It might be assumed that, besides the use of immunotherapy, other aspects pertaining to disease biology, host-disease interaction and treatment may have played a role. Indeed, this relatively long-lasting disease control under chemotherapy may have been a sign of a pre-existing underlying immune response against an immunogenic tumor, possibly enhanced through the abscopal effect induced by the radiotherapy treatments.

Another aspect worthy of discussion is the frequency and severity of the immune-related adverse events (irAEs) that arose during treatment. Multiple authors have reported improved outcomes in patients who manifest irAEs compared to those who do not manifest irAEs, mainly in the setting of non-small cell lung cancer (NSCLC).[5-7] Whether or not increasing immune checkpoint inhibitor dosage and/or treatment duration to the point that they are more likely to result in some irAEs would lead to an overall clinical benefit, however, remains to be determined.

CONCLUSIONS

Though anecdotal, the reported case exemplifies not only the possibility of sustained response to immune checkpoint inhibition in patients with SCLC but also the wide spectrum of possible toxicities and their impact on quality of life. Further research is needed to identify appropriate biomarkers for patient selection.

Conflict of interest

The authors declare no conflicts of interest relevant to this manuscript.

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