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CASE REPORT

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Long-term remission of small cell lung cancer after reactivation of tuberculosis following immune-checkpoint blockade: A case report

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Abstract

Immune-checkpoint inhibitors (ICIs) provide a promising treatment option for advanced tumors including small cell lung cancer (SCLC). Nevertheless, in addition to immune-related adverse events (irAEs), an increased risk of infection including tuberculosis has been previously described. Here, we report a case of long-term remission of a patient with SCLC after reactivation of lung tuberculosis following ICI therapy. Our case illustrates the complexity of ICI-associated immune modulation in tuberculosis. Since new lesions in lung cancer patients are commonly associated with tumor progression, infections with mycobacterial tuberculosis may be underdiagnosed in lung cancer.

KEYWORDS
immune-checkpoint inhibitors, lung cancer, PD-L1, tuberculosis

INTRODUCTION

Small cell lung cancer (SCLC) is characterized by its high proliferative capacity and a high tendency to relapse after initial remission upon treatment with cytotoxic therapy. SCLC has a poor prognosis with a five-year survival rate of only 7%.[1] SCLC is commonly associated with smoking and a subsequent high tumor mutational burden (TMB), as well as TP53 and retina blastoma protein (RB) mutations.[2,3] Although conventional platinum/etoposide-based chemotherapy commonly results in striking tumor remissions, long-term tumor control is a rare event.[4] Antibodies targeting the immune-checkpoint molecules PD-1/PDL-1 and CTLA4 have shown promising results in SCLC.[5,6] In addition to immune-related adverse events (irAEs), a known side effect of such therapies is the increased risk of infectious diseases including tuberculosis (TBC).[7,8] Here, we report on a rare case of a long-term remission of a young SCLC patient after reactivation of lung tuberculosis following combined immune-checkpoint blockade.

CASE REPORT

A 44-year-old man with a smoking history of 15 pack-years was admitted to hospital complaining of recurrent episodes of cough and progressive dyspnoea. A diagnostic work-up showed an extensive tumor mass in the right lung, originating from the upper lobe with infiltration of the middle and lower lobes. Histopathological analysis revealed the diagnosis of a small cell neuroendocrine tumor with a proliferation index (Ki67) of 80%. Upon confirmation of extensive disease stage (cT4, cN2, cMx), the patient underwent six cycles of palliative chemotherapy with cisplatinum/etoposide followed by radiotherapy of the primary tumor location with 42 Gy.

Twelve months after radiotherapy, the patient's general condition decreased rapidly and a computed tomography

(CT) scan revealed a tumor relapse in the middle lobe of the right lung. A biopsy of the pulmonary lesion confirmed the diagnosis of the SCLC histopathologically. Genetic profiling was subsequently performed and showed a high mutational burden (up to 1166 missense variants), as well as alterations in TP53 (c.671_672insTTTGA, p.E224D*fs**25 and loss of wild-type allele) and RB1 (c.2501C > G, p.S834*); two phenotypic mutations found in small cell cancers.[9,10] In addition, a BRCA1 (c.1529C > T; p.S510L and loss of wild-type allele) mutation was identified. A second-line therapy with the topoisomerase inhibitor topotecan failed after six cycles and resulted in a further progress of the central pulmonary tumor site (Figure 1a). Unfortunately, a cMRI-scan revealed multiple cerebral lesions (Figure 1b). Radiotherapy to the brain (30 Gy) was concurrently administered. In consideration of the high mutational burden, combined immunotherapy with nivolumab and ipilimumab was initiated.[5]

After three cycles of ICIs, a CT scan showed a relevant decrease in the central pulmonary mass (Figure 1a). However, a new lesion in the left and right upper lobe was demonstrated (Figure 1c). Laboratory tests showed elevated C-reactive protein plasma levels (8–10 mg/dl, normal range up to 0.5 mg/dl) (Figure 1e). Interestingly, at this time, the patient presented with no clinical symptoms such as persistent cough or signs of clinical deterioration. Several enlarged mediastinal lymph nodes were associated with lymph node metastasis of the underlying SCLC. Bronchoscopy revealed a large cavity in the area of the left upper lobe connected to the bronchial system (Figure 1d). A Ziehl-Neelsen (ZN) stain of the bronchoalveolar lavage showed a positive result for mycobacteria. In addition, a positive polymerase chain reaction of mycobacteria tuberculosis (MTB) was detected. Subsequently performed acid-fast bacillus staining confirmed positive results in sputum samples and gastric lavage. Of note, a quantiferon test performed by a pneumologist prior to

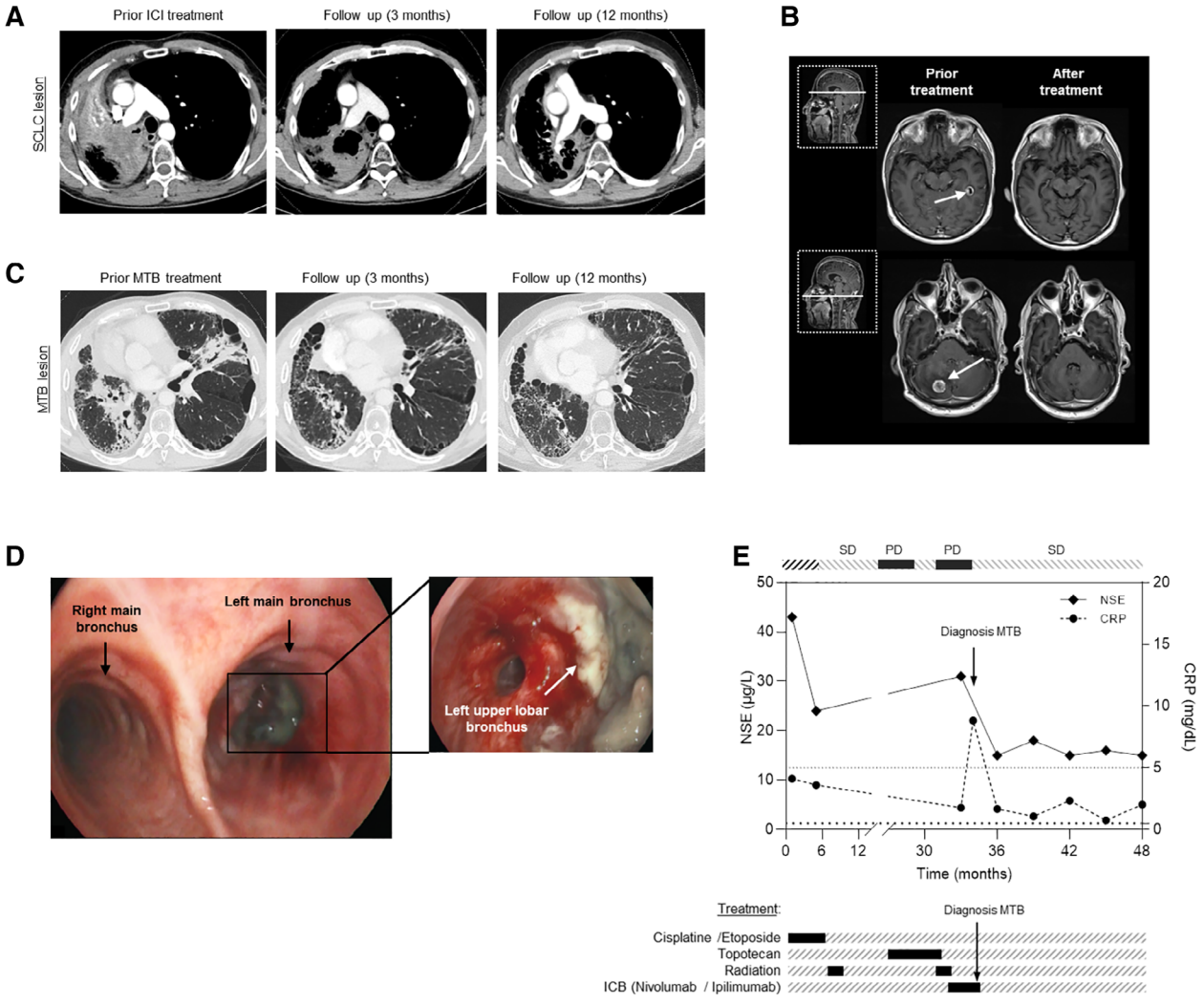

FIGURE 1 Clinical presentation of the SCLC patient and treatment scheme. (a) CT scan of the pulmonary SCLC lesion before and after ICI treatment. (b) Assessment of brain metastasis (white arrow) via cMRI prior to ICI treatment and after six months. (c) CT scan of the pulmonary MTB lesion before and after anti-infective treatment. (d) Bronchoscopy of the primary MTB lesion in the left upper bronchus. (e) Neuron specific enolase (NSE) and CRP levels during the entire treatment (PD, progressive disease; SD, stable disease)

diagnosis of SCLC was negative. Susceptibility testing showed sensitivity to all tested antimycobacterial agents, beyond termination of ICI treatment, and a four-drug combination of isoniazid, rifampicin, ethambutol, and pyrazinamide was commenced. After completion of this anti-infective therapy, a relevant decrease in the size of both lung lesions was observed (Figure 1c), and the cerebral metastases were no longer detectable (Figure 1b).

Remarkably, without any further treatment, several CT scans showed no signs of tumor progression. To date, 24 months after the last treatment with ICIs, the patient shows a highly favorable physical condition as well as stable disease of all former detectable tumor manifestations.

DISCUSSION

The case presented here illustrates the concomitance of an active MTB infection upon ICI therapy and a prolonged remission of an advanced SCLC. Interestingly, reactivation of tuberculosis in cancer patients undergoing treatment with ICIs has been reported in a small number of cases.[7] In contrast to other infectious complications upon ICI treatment, which are commonly related to immune inhibitory treatment to control irAEs, exacerbation of MTB does not seem to be correlated with the use of corticosteroids or TNF inhibitors.[7] Even in our case, no irAE was detected or a subsequent immune inhibitory treatment administered. As a result, MTB reactivation might be directly correlated to ICI treatment. However, the underlying mechanisms triggering the reactivation in this context are only partially understood.

The role of T cells in MTB infections has been investigated in several preclinical models and showed that $CD4^+$ T cells (Th1) play a major role in mycobacterial infections.[11–13] In contrast to data showing that blocking of PD-1/PD-L1 can partially prevent T cell exhaustion and subsequently restore T cell activity, lack of PD-1 in MTB-specific effector $CD4^+$ T cells led to dysregulated IFN-γ production and fatal immune-mediated pathology.[14] In virus-specific $CD8^+$ T cells, PD-1 knockdown (PD-1−/−) led to a deeper T cell exhaustion compared to PD-1 wild-type.[15] In addition, PD-1−/− mice had more severe and sometimes lethal causes of MTB infection.[12,16] These observations highlight the complex role of inhibitory immune-checkpoint signaling mediating T cell exhaustion and immune surveillance during infections and cancer. Nevertheless, more data are urgently needed to better understand the particular role of ICI in MTB.

Our case, however not only describes a reactivation of MTB. We also observed a long-term remission of the underlying tumor disease. Accordingly, the question arises whether the reactivation of MTB might additionally contribute to long-term cancer immunosurveillance. It is known that TBC pathogens stimulate the activation of both innate and cellular immunity via different classes of cytokines.[17] Since mycobacteria associated antigens have also been described to enforce the antitumor immune response, a contribution of MTB to cancer immunosurveillance may be conceivable.[18] Hereby, it might be speculated that the exacerbation of MTB stimulated the host's immune response, thus leading to a reinforcement of the antitumor immune activity. This particular effect might be further enhanced after PD-1/CTLA4 inhibition. However, more clinical and preclinical evidence is needed to prove such a hypothesis. Interestingly, an improved survival in non-small cell lung cancer (NSCLC) patients affected by active tuberculosis compared to nonaffected NSCLC patients has already been described.[19]

In summary, our case highlights the complex orchestra of immunomodulation in infection and cancer. Due to the fact that radiological signs of MTB including mediastinal or hilar lymphadenopathy, infiltrates, consolidations or cavities are commonly observed in lung cancer patients, diagnosis of MTB in lung cancer patients remains challenging. Moreover, since new lesions in lung cancer patients are commonly associated with tumor progression, MTB infections associated with ICIs might be underdiagnosed. As a consequence, specific testing for MTB in cancer patients receiving ICIs might be beneficial, even without strong clinical evidence.

In conclusion, this case report in a patient with long-term remission of SCLC after infection with mycobacteria tuberculosis following immune-checkpoint inhibitor (ICI) therapy emphasizes the need for further investigation of the complex crosstalk of ICI treatment, infection and cancer.

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