

[CASE REPORT]

Neuropsychiatric Immune-related Adverse Events Induced by Pembrolizumab in a Patient with Lung Adenocarcinoma and Systemic Lupus Erythematosus

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Abstract:

The patient was a 73-year-old woman with lung adenocarcinoma and systemic lupus erythematosus (SLE) who was treated with pembrolizumab. After six cycles of pembrolizumab, she developed symptoms suggestive of neuropsychiatric SLE, such as resting tremor, confusional state, depression, mood disorder, and anxiety disorder. In addition, her cerebrospinal fluid level of interleukin-6 was elevated. Her symptoms resolved one month after the discontinuation of pembrolizumab. This is the first report of neuropsychiatric symptoms in a patient with lung cancer and SLE on immune checkpoint blockade therapy.

Key words: neuropsychiatric immune-related adverse events with pembrolizumab, non-small cell lung cancer with SLE

(Intern Med 59: 569-572, 2020)

(DOI: 10.2169/internalmedicine.3782-19)

Introduction

The development of immune checkpoint blockade (ICB) therapy represents dramatic progress in the treatment of advanced non-small cell lung cancer (NSCLC). Anti-programmed cell death 1 (PD-1) monoclonal antibodies (mAbs), such as nivolumab and pembrolizumab, and anti-programmed death-ligand 1 (PD-L1) mAbs, such as atezolizumab and durvalumab, counteract molecule-mediated immunosuppressive signals. They have become key immune checkpoint inhibitors (ICIs) (1-3). The addition of ICB therapy to standard chemotherapy has resulted in significantly longer overall survival and progression-free survival in comparison to chemotherapy alone in many patients with previously untreated metastatic NSCLC (4-6).

Despite their benefits, reports of immune-related adverse events (irAEs) in association with ICB therapy are accumulating (1, 2, 7). Although a multi-institutional retrospective analysis suggested that ICIs could be safely administered to

patients with NSCLC and a history of autoimmune disease (AID) (8, 9), their safety and efficacy in patients with NSCLC and systemic lupus erythematosus (SLE) have not been extensively studied. We herein present the case of a patient with lung cancer and SLE who experienced neuropsychiatric symptoms after treatment with pembrolizumab, which was suspected to be an irAE similar to neuropsychiatric SLE (NPSLE).

Case Report

The patient was a 73-year-old woman who had been diagnosed with T4N2M1b adenocarcinoma of the lung in July 2017 (Fig. 1). At 68 years of age, she was diagnosed with SLE based on arthritis, pleuritis, and elevated levels of anti-nuclear and anti-dsDNA antibodies. She was being treated with prednisolone (5 mg/day) and tacrolimus (1 mg/day) at the time of the lung cancer diagnosis. Her tumor showed a high PDL-1 expression level (Tumor Proportion Score >50%). She began pembrolizumab therapy in August 2017

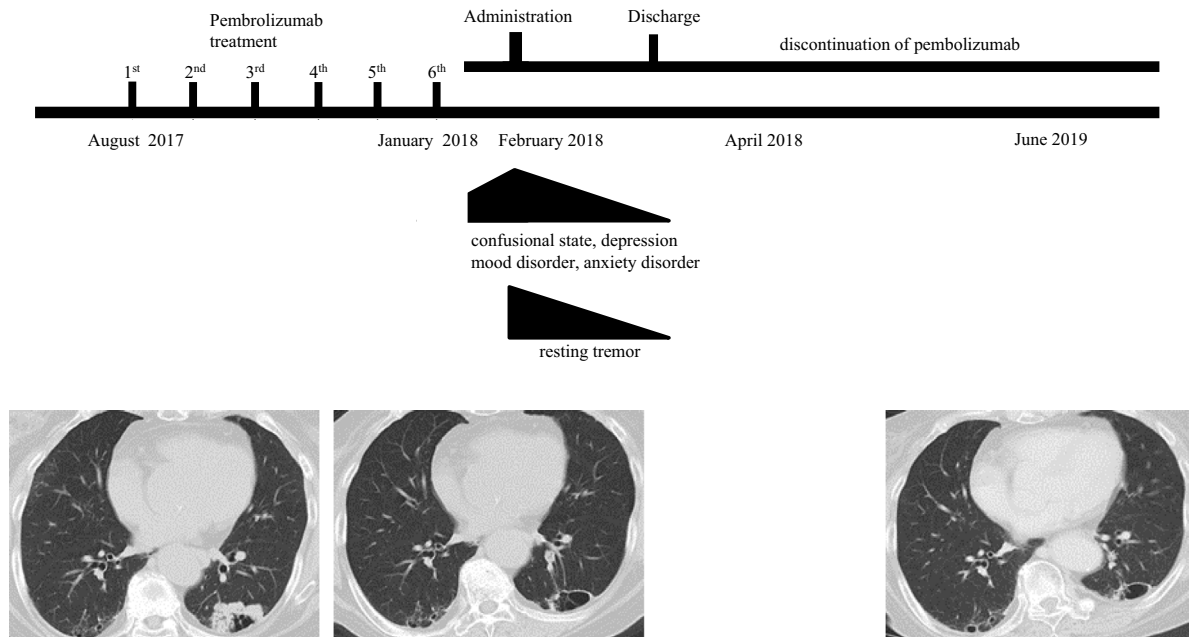


Figure 1. Clinical course. Pembrolizumab has shown great promise in the treatment of non-small cell lung cancer. After six cycles of pembrolizumab injection, the patient developed neuropsychiatric symptoms, including resting tremor, confusional state, depression, mood disorder, and anxiety disorder. At 15 months after the discontinuation of pembrolizumab, chest CT showed a complete response.

(Fig. 1) and had no symptoms at the time of the initiation of pembrolizumab. A chest computed tomography (CT) scan revealed a complete response; however, the patient experienced resting tremor (Common Terminology Criteria for Adverse Events grade 1), acute confusional state (grade 3), depression (grade 3), mood disorder (grade 3), and anxiety disorder (grade 3) after six cycles of pembrolizumab (Fig. 1). She was admitted to our hospital in February 2018. A neurological examination revealed increased biceps and patellar reflexes and bilateral postural tremors in the fingers (frequency, 4-5 Hz). Electroencephalography showed slow waves of 3-4 Hz, indicating a decreased frontal lobe function (Fig. 2). CT and magnetic resonance imaging (MRI) of the head revealed no evidence of cerebrovascular accident, brain metastases, or carcinomatous meningitis. Cerebrospinal fluid (CSF) cultures were negative and malignant cells were not detected, which ruled out infection and carcinomatous meningitis. An analysis of the patient's CSF revealed an increase of total cells (31 cells/ μ L), which included monocytes and lymphocytes. Notably, the interleukin-6 (IL-6) level in the CSF was elevated (27.8 pg/mL, reference value <4.3 pg/mL). Blood tests revealed little change in the serum complement levels and anti-double stranded DNA antibody titers. We suspected that these neuropsychiatric symptoms were irAEs induced by pembrolizumab, similar to NPSLE. Pembrolizumab was discontinued. The resting tremor, acute confusional state, depression, and mood disorder resolved within 1 month after the discontinuation of pembrolizumab therapy. Furthermore, she was already treated with prednisolone (5 mg/day) and tacrolimus (1 mg/day), so we did not increase the steroid dosage or add other immunosuppressant

after the development of the severe irAE. At fifteen months after discontinuation, chest CT showed no recurrence of lung cancer (Fig. 1). The patient's neuropsychiatric symptoms did not recur, even without specific additional treatment.

Discussion

NPSLE refers to neuropsychiatric involvement in SLE, which affects the central nervous system, peripheral nervous system, or both (10). NPSLE is clinically heterogeneous and therefore difficult to diagnose (11). The precise pathophysiology of NPSLE is not clearly understood. Due to a lack of specific diagnostic biomarkers, the diagnosis of NPSLE is still based on clinical observations, laboratory tests, and imaging techniques (12). For the diagnosis of NPSLE, the nomenclature system proposed by the American College of Rheumatology (ACR) in 1999 is widely accepted, which provides the criteria for 19 neuropsychiatric manifestations (13). Furthermore, infection, trauma, malignancy, and other neurological diseases should be ruled out (14). Among the manifestations listed by the ACR, our patient had acute confusional state, anxiety disorder, and mood disorder. Cerebrovascular events and cranial metastases were excluded based on CT and MRI findings.

Various autoantibodies might play different pathogenic roles in the development of NPSLE symptoms by targeting diverse cellular or tissue components. Autoantibodies can activate downstream signaling cascades, leading to the expression of various cytokines and chemokines (15). Elevation of IL-6 levels in the CSF (≥ 4.3 pg/mL) is regarded as a highly

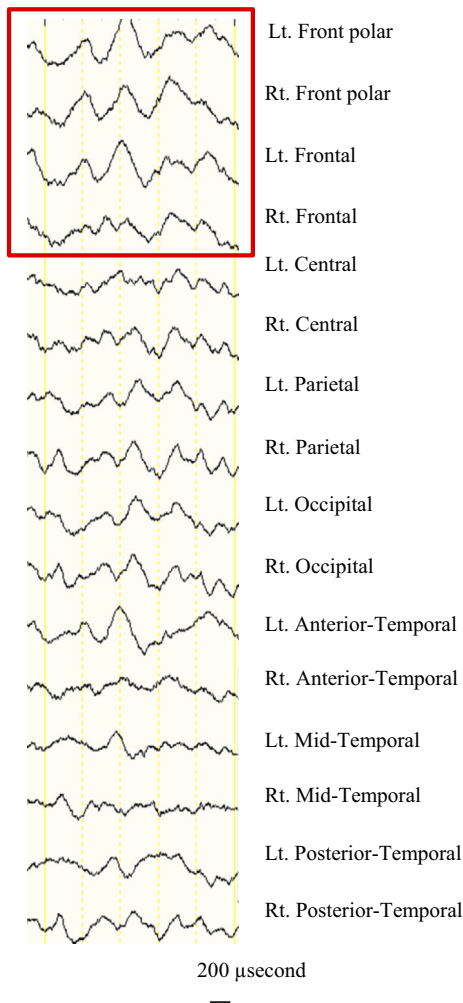


Figure 2. Electroencephalography. Red flame indicates waves of 3-4 Hz indicating a decreased frontal lobe function.

specific and sensitive finding for NPSLE (87.5% and 92.3%, respectively) (16). Our patient's CSF IL-6 level was high (27.8 pg/mL), which might have been related to her neuropsychiatric manifestations. Thus, we presume that pembrolizumab was responsible for the progression of NPSLE-like symptoms in our patient.

PD-1 binds to its two ligands, PDL-1 and PDL-2, and mediates signals that prevent immune surveillance and autoimmunity by inactivating cytotoxic T cells (17). Blockade of PD-1 activates lymphocytes and might induce their transmigration into the central nervous system (CNS). Indeed, the increased transmigration of both of CD4 and CD8 T lymphocytes through endothelial cells was observed in blood vessels in the human brain after PDL-1 or PDL-2 blockade (18). In our patient, pembrolizumab might have induced the migration of lymphocytes into the CNS, leading to inflammation and the overproduction of cytokines including IL-6. Furthermore, Chipman et al. reported that IL-6 blockade was a therapeutic option for the management of steroid refractory irAE, including neuropsychiatric irAE (19), so it is conceivable that an increased IL-6 level is significantly associated with the development of irAEs, including neuropsychiatric irAEs. We believe that such neurological irAEs

might result from pathophysiological mechanisms similar to those in NPSLE.

In a multi-institutional retrospective analysis, Giulia et al. reported that adverse events in patients with NSCLC and AID who were treated with ICIs were generally manageable. Among 56 patients with NSCLC and AID who received ICIs, 13 patients (23%) experienced an exacerbation of AID. Four of them were treated with systemic corticosteroids, but none required permanent discontinuation of ICIs (8). Likewise, Abdel-Wahab et al. reported that exacerbations of AID can be managed without discontinuing ICB therapy because many severe or fatal events resolve after the administration of systemic corticosteroids (20). Patients with SLE were included in these clinical studies, but no systemic or neurological exacerbations were reported. In our case, we decided to discontinue pembrolizumab. Despite this, the primary and metastatic tumors did not progress. Further studies are required to evaluate the safety and efficacy of ICIs in patients with NSCLC and SLE.

In conclusion, this is the first report of a patient with SLE who developed neurological irAEs after ICB therapy. Mechanisms similar to those in NPSLE could be involved. It is necessary to be aware of the risk of irAEs affecting the CNS when treating patients with NSCLC and SLE.

The authors state that they have no Conflict of Interest (COI).

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