Immune-related encephalitis in two patients treated with immune checkpoint inhibitor

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Introduction

The use of immune checkpoint inhibitors (ICIs) in solid oncology is increasing at a fast pace in modern oncology (melanoma, lung carcinoma, renal carcinoma, urothelial cancer, head and neck cancer, breast cancer). The action of ICIs (anti-PD1/PD-L1 and anti-CTLA4) is based on the activation of T cells to destroy tumor cells by reversing tumor-induced immunosuppression [1]. However, the uncontrolled activation of T cells can lead to a disruption of immune tolerance, leading to immune-related adverse events (irAEs) that could affect many organs [2]. The most common irAEs are gastrointestinal (colitis), cutaneous (maculopapular rash), endocrine (dysthyroidism), hepatic and pulmonary complications. Neurological irAEs are rare complications that are poorly known and are revealed by nonspecific symptoms. Authentic neurological syndromes have been described with rapid evolution and poor prognosis [2–4]. Notably, only a few cases of dysimmune encephalitis have been reported in the literature to date [5]. Here, we report two cases of immune-related encephalitis in two patients treated with ICIs for metastatic non-small-cell lung cancer (NSCLC).

Case report

A 48-year-old woman who smoked was diagnosed on February 2018 with metastatic lung adenocarcinoma in the context of increasing dyspnea and articular pain. PD-L1 expression was evaluated in 20% of tumor cells, and a mutation in *KRAS* (Ex2 c.34G>T p.(Gly12Cys)) was documented. She was included in a first-line immunotherapeutic phase II/III trial (B-FAST) and was randomized in experimental cohort C, in which the allocated treatment was atezolizumab (anti-PD-L1) at a dose of 1200 mg by intravenous infusion. She received the first atezolizumab injection in April 2018. Thirteen days after the first

immunotherapy injection, she was hospitalized for a persistent fever despite the introduction of amoxicillin/clavulanic acid. On day sixteen, she presented nonspecific neurological symptoms such as psychomotor slowdown, temporospatial disorientation, memory impairment and aphasia. Biological workup revealed an elevation of C-reactive protein (CRP), anemia (11.4 g/dL), lymphopenia (700/mm^3), and hyponatremia (129 mmol/L). The results of coagulation and hepatic and renal tests were normal. Lumbar puncture (LP) revealed meningitis (62 nucleated cells/mm^3) with mixed formula (neutrophils predominant over lymphocytes) and elevated protein and glucose. No malignant cells were found in the cerebrospinal fluid. Brain MRI and electroencephalogram were normal. In the context of febrile meningoencephalitis, antibiotics were introduced with cefotaxime/amoxicillin, acyclovir and dexamethasone, despite broad-range microbiological and cytological exploration results being negative. Atezolizumab was stopped, and high-dose steroids were introduced (methylprednisolone 1 gram/day for 3 days then 1 mg/kg/day for one month followed by a very gradual decrease). A second LP 48 hours after the start of steroid treatment confirmed lymphocyte-predominant (54%) meningitis, and a new MRI revealed pachy- and leptomeningitis (Figure 1A). Evolution was favorable with complete resolution of neurological symptoms and brain MRI abnormalities in March 2019 (Figure 1B). Immunotherapy was then substituted by chemotherapy (carboplatin/pemetrexed) plus bevacizumab. The disease progressed despite two more lines of chemotherapy. Currently, the patient is being rechallenged with pembrolizumab (anti-PD1) under close clinical follow-up. No irAEs were observed after one month of treatment.

A 57-year-old man who was a former smoker with a vascular medical history (myocardial infarction in 2007, hypertension, dyslipidemia, moderate obesity) was diagnosed in August 2017 with metastatic (pericardial and pulmonary) lung adenocarcinoma. PD-L1

expression was higher than 50%, and no alteration was found for the *EGFR*, *ALK*, *ROS1* or *RET* genes. First-line pembrolizumab was introduced in September 2017. The patient experienced myalgia and folliculitis after the third immunotherapy administration, requiring the introduction of topical steroid treatment, followed by oral steroids (prednisolone 10 mg/day). In January 2018, the patient was hospitalized for neurological symptoms (confusion, temporospatial disorientation, memory loss) with grade 2 diarrhea. LP showed lymphocytic meningitis (elevated cerebrospinal fluid protein level at 1.41 g/L; 40 nucleated cells/mm^3 with 98% lymphocytes) and no sign of microbiological infection. Antineuronal antibodies were negative, and no malignant cells were found in the cerebrospinal fluid. Brain MRI showed limbic encephalitis (Figure 2A), and the electroencephalogram was normal. Pembrolizumab was discontinued, and high-dose steroids were introduced (methylprednisolone 1 gram/day for 3 days then 1 mg/kg/day for one month, followed by very gradual decrease), allowing slowly favorable clinical evolution. A complete resolution of brain MRI abnormalities was observed after 3 months (Figure 2B), and the patient recovered completely from the neurological symptoms after six months. The tumor has remained stable more than two years after the discontinuation of immunotherapy (without the reintroduction of specific treatment).

Discussion

Neurological irAEs are uncommon complications of ICI use, with an overall incidence ranging from 2% to 4%, and grade 3-4 toxicities are rare (<1%) [2]. In the 2017 ESMO Guidelines, the incidence for all grades was 1% [6]. A review of the literature of 59 trials (9208 patients) found a higher incidence of neurological irAEs depending on the type of ICI and the use in monotherapy or in combination: 3.8% with anti-CTLA4, 6.1% with anti-PD1 and 12% with anti-PD1 and anti-CTLA4 in combination [7]. The time to the onset of neurological irAEs

varies from 6 to 13 weeks after the initiation of ICI, but neurological irAEs may appear at any time during treatment and even after discontinuation.

Neurological irAEs have various clinical presentations, making their diagnosis and treatment difficult. The central and/or peripheral nervous systems may be affected. Grades 1-2 are usually nonspecific, such as asthenia, headaches, dizziness, paresthesias, dysgeusia, etc. Grades 3-4 are more frequently authentic neurological syndromes, such as myasthenia gravis, Guillain Barré syndrome, chronic inflammatory polyneuropathy, myelitis, aseptic meningitis, encephalitis or posterior-reversible encephalopathy. Of note, peripheric neuropathy prevails in the literature [2,4,6,8,9]. Clinical presentations are often unusual. No markers or antibodies are identified to confirm diagnosis (elimination diagnosis). Neurological irAEs might evolve dramatically and engage vital prognosis.

The exact physiopathology of irAEs remains unclear. The inhibition of PD1 and CTLA4 stimulates antibody production and can therefore lead to antibody-mediated autoimmune disease. In a phase II trial assessing the efficacy of ipilimumab in combination with chemotherapy in the treatment of metastatic small-cell lung cancer, the detection of autoantibodies was systematically performed at baseline. Among 42 patients, 60.5% had autoantibodies, of which 45% had antineuronal antibodies. A post hoc analysis showed that the presence of autoantibodies had a tendency to improve survival. The presence of antineuronal antibodies was correlated with more irAEs and especially neurological toxicity [10]. Another retrospective analysis with 137 patients treated with anti-PD1 (nivolumab or pembrolizumab) for metastatic NSCLC showed an improvement in progression-free survival (PFS) in patients with antineuronal antibodies compared to those without [11].

A review of the literature about serious neurological irAEs with ICIs (nivolumab alone or in combination with ipilimumab) published in 2017 [5] included 12 clinical trials, with 3763 patients treated with ICIs for metastatic melanoma. Thirty-five out of 3763 patients had

serious neurological irAEs (0.93%), the median age was 63.5 years, and the population was mostly men (74%). Serious irAEs included neuropathy (N=22), noninfective meningitis (N=5), encephalitis (N=6), neuromuscular disorders (N=3), and nonspecific events (N=7; including headaches, seizure, confused state, syncope). Seven patients had multiple neurological irAEs, with 5 receiving nivolumab and ipilimumab in combination. In the 6 cases of encephalitis (<0.2%), the median time to onset was 51,5 days (ranging from 18 to 297 days). The symptoms were multiple, such as confusion, aphasia, agitation, difficulty walking, seizure and asthenia. ICIs were stopped for 5 patients, and 1 patient died from complications of encephalitis. All patients received a high dose of steroids, 3 patients received intravenous immunoglobulin injections due to steroid ineffectiveness, and 1 patient received cyclophosphamide associated with rituximab. The majority of patients were treated with empiric antibiotics and antivirals, and 3 patients received antiepileptic treatments. Four patients had total resolution of the neurological symptoms, 1 patient required six months of rehabilitation for symptom improvement, and 3 patients had a partial or complete response with ICIs.

Dysimmune encephalitis is a therapeutic emergency and remains a diagnosis of exclusion. Hospitalization is required, often in an intensive care unit. The first step in the diagnosis of dysimmune encephalitis is to consider differential diagnoses: infectious encephalitis (bacteriological and viral), other causes of encephalitis (toxic or metabolic), infectious meningitis, carcinomatous meningitis, brain metastasis, intracranial hypertension, brain abscess, and cerebral venous thrombosis. Complementary examinations are essential: complete biological assessment, viral serologies in the blood and cerebrospinal fluid, the determination of antineuronal antibodies, brain MRI, lumbar puncture and electroencephalogram. Specialized neurological care is essential for diagnosis and follow-up. The treatment is based on the suspension and often the definitive discontinuation of ICIs, high

doses of steroids (methylprednisolone or an equivalent 1 gram/day for 3 days then 1 mg/kg/day for one month followed by very gradual decrease). Other immunosuppressive therapy can also be used (IV immunoglobulins, rituximab, etc.). Empirical treatment with antibiotics, antivirals and antiepileptics is usually introduced early [5,6,12].

Conclusion

With the increase in ICI indications in solid oncology, it is critical for clinicians to recognize irAEs. Neurological irAEs, particularly dysimmune encephalitis, remain rare complications, but they are increasingly described in the literature. The nonspecificity of initial symptoms makes the diagnosis of neurological irAEs difficult. However, neurological irAEs may evolve dramatically and engage vital prognosis. Therefore, it is essential for thoracic oncologists to be aware of these neurological irAEs and diagnose them early to provide prompt management.

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Figure legend:

Figure 1:

A. Brain MRI, axial and coronal section, T2 FLAIR. Diffuse meningeal thickening and hyperintensity of the left insular cortex (white arrows).
B. Brain MRI, axial section, T2 FLAIR sequence. Complete resolution of diffuse meningeal hyperintensities.

Figure 2

A. Brain MRI, axial section, T2 FLAIR sequence. Bilateral hyperintensity of the medial temporal lobes, predominantly on the right side, evoking limbic encephalitis (white arrows).
B. Brain MRI, axial section, T2 FLAIR sequence. Complete resolution of temporal lobe hyperintensities.

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Dr. Robert has nothing to disclose.

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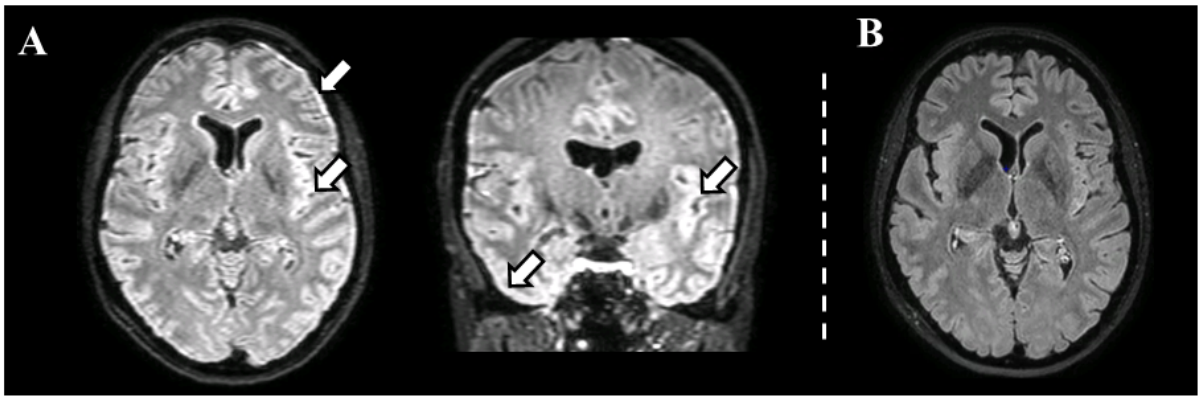

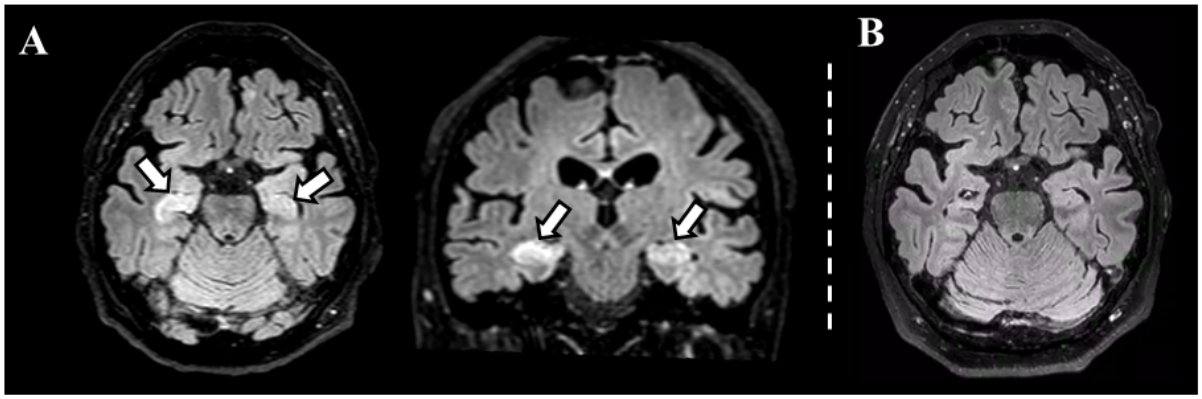

Clinical Practice Points:

- Dysimmune encephalitis remains a rare complication of immune checkpoint inhibitors treatment

- The variability and non-specificity of symptoms could be clinically challenging

- Prompt recognition and corticosteroid therapy usually allow complete recovery

- Thoracic oncologists should be aware of this rare but severe toxicity of immune checkpoint inhibitors