Acta Neurologica Belgica
https://doi.org/10.1007/s13760-019-01179-3

LETTER TO THE EDITOR

Anti-Ma2/Ta paraneoplastic rhombencephalitis in a patient with lung cancer responsive to anti-PD1 therapy

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Received: 22 January 2019 / Accepted: 27 June 2019

Immune checkpoint inhibitors (ICPIs) are effective and promising in the treatment of metastatic cancers. They include anti-programmed cell death 1 (PD-1), anti-PD ligand 1 (PDL1), and anti-cytotoxic lymphocyte-associated protein 4 (CTLA4) monoclonal antibodies (mAbs). However, ICPI-induced T-cell activation can also cause autoimmune adverse events in many host organs, including the nervous system [1, 2]. We report on a patient who developed an anti-Ma2/Ta rhombencephalitis associated upon treatment of a metastatic non-small cell lung cancer responsive to *pembrolizumab,* an anti-PD-1 mAb.

A 69-year-old man was diagnosed with metastatic non-small cell lung cancer. The initial work up revealed two pulmonary nodular lesions located in the right inferior and in the apical segment of the left inferior lobes. They were associated with mediastinal adenopathies and a solitary left cerebellar metastasis (stage IV, N2 M1b). ALK and EGFR mutations were absent and 100% of the neoplastic cells expressed PDL-1. Following administration of 10 cycles of *pembrolizumab* every 3 weeks, PET scan and magnetic resonance imaging (MRI) studies revealed a dramatic volume reduction of both the cerebellar and the pulmonary tumoral lesions. However, 1 month later, the patient developed a subacute cerebellar gait ataxia with left gaze oculomotor palsy and upbeat vertical nystagmus. He did not have any nutritional disorder. MRI showed a T2 and Flair hyperintense lesion within the pontine tegmentum (Fig. 1). High serum titers of anti-Ma2/Ta antibodies confirmed the diagnosis of anti-Ma2 paraneoplastic rhomboencephalitis. Detection of serum anti-Ma1 antibodies and cerebrospinal fluid examination was not performed. *Pembrolizumab* was stopped. He received a 5 day-course of intravenous methylprednisolone (1 g per day) followed by a slow tapering down of oral prednisolone without beneficial effect. His neurological condition continued to deteriorate despite 3 cycles of rituximab. He developed an acute respiratory distress and died 3 months after the onset of the neurological symptoms, without recurrence of the lung cancer.

Anti-Ma2/Ta antibody-associated paraneoplastic neurological disorders (PND) mostly affect the limbic system, diencephalon, and brain stem. The anti-Ma2 subtype occurs in younger patients with a better prognosis than the Ma1/Ma2 subtype. The most frequent associated cancers are testicular germ-cell tumor in the Ma2 subtype and non-small cell lung cancer in the Ma1/Ma2 subtype. Other associated tumors include lung, digestive tract, renal, bladder and ovarian adenocarcinoma, as well as non-Hodgkin lymphoma [3, 4]. In about two-thirds of the patients, the PND precedes the diagnosis of the tumor [3, 4]. In our case, the PND occurred several months after the diagnosis of the lung carcinoma, despite a favorable anti-tumoral response to the immunotherapy. *Pembrolizumab* is a human monoclonal antibody that blocks the interaction of PD-1 with its PDL-1 and PDL-2 ligands. PD-1 is an immune-inhibitory receptor expressed on cells of the immune system including B- and T-lymphocytes. Binding of PD-1 to its ligand inhibits a cytotoxic T-cell response, therefore, allowing cancer cells to escape immune surveillance. *Pembrolizumab* blocks the interaction of PD1 with cancer cells that upregulate PDL-1 and PDL-2, thereby facilitating tumor recognition by cytotoxic T cells. Serious neurological adverse events occur in 0.2–0.4% of the patients treated with anti-PD1-Abs, such as pembrolizumab an nivolumab. They include inflammatory myopathies, myasthenia gravis, vasculitis, neuropathies, aseptic meningitis, autoimmune encephalitis, multiple sclerosis, and hypophysitis [3, 4]. ICPI-triggered autoimmune diseases evolve rapidly and occur at all stages of ICPI

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Published online: 01 July 2019

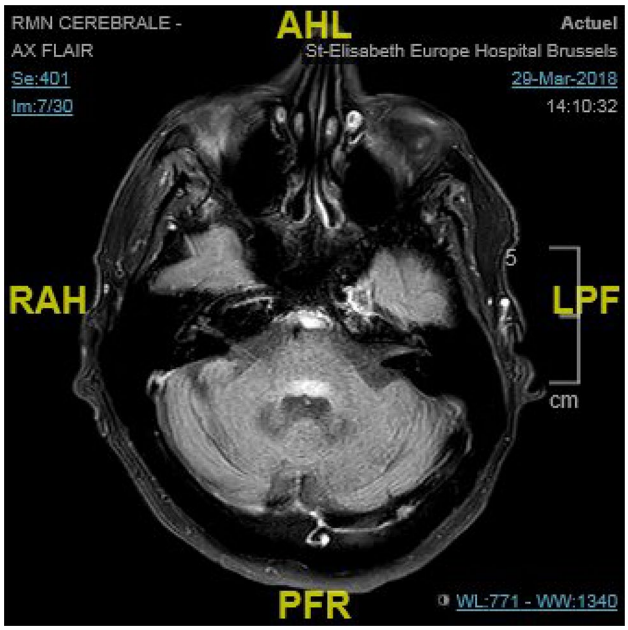

Fig. 1 Brain MRI: tegmental pontine lesion, hyperintense on FLAIR

treatment, in contrast to the slow evolution of the immune-mediated PND [2]. ICPIs could also theoretically promote PND. Acute limbic encephalitis with anti-Ma2/Ta Abs has been already reported in a Hodgkin lymphoma patient early in the course of nivolumab therapy [1]. In our patient, T-cell activation induced by *pembrolizumab* probably revealed a latent anti-Ma2/Ta PND. Such major adverse event must be managed by prompt discontinuation of the ICPI and initiation of aggressive immunosuppression with corticosteroids and eventually followed by rituximab or plasmapheresis.

ICPIs represent a novel and promising therapy for metastatic cancers. However, they can induce or unmask latent autoimmune disorders, including PND. We recommend a preventive screening of onconeuronal antibodies in the serum before initiation of an ICPI therapy. Such therapies could be avoided in patients with a positive onconeuronal serology and/or a PND.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors declare that they acted in accordance with the 1964 Declaration of Helsinki. This article does not contain any studies with human participants by any of the authors.

Informed consent The informed consent was obtained from the family members of the patient.

References

1. Fellner A, Makranz C, Lotem M et al (2018) Neurologic complications of immune checkpoint inhibitors. J Neurol Oncol. https://doi.org/10.1007/s11060-018-2752-5
2. Dalakas MC (2018) Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. Ther Adv Neurol Disord 11:1–9
3. Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR (2004) Clinical analysis of anti-Ma2-associated encephalitis. Brain 127:1831–1844
4. Ortega-Suero G, Sola-Valls N, Escudero D, Saiz A, Graus F (2018) Anti-Ma and anti-Ma2-associated paraneoplastic neurological syndromes. Neurologia 33:18–27