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LETTER TO THE EDITORS

Multiple sclerosis associated with pembrolizumab in a patient with non-small cell lung cancer

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Dear Sirs,

Pembrolizumab is a humanized IgG4 anti-programmed cell death-1 (PD-1) antibody serving as an immune-checkpoint inhibitor and proved long-lasting responses and prolonged survival for the treatment of advanced non-small cell lung cancer (NSCLC). PD-1 and its ligands (PD-L1 and PD-L2) are negative co-stimulatory molecules of T-cell activation. Pembrolizumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, in this way, it enhances antitumor immune response directed at a variety of cancers [1]. In patients with PD-L1 > 50%, pembrolizumab has revolutionized the prognosis conferring a four-fold increase of survival compared to chemotherapy, with few, mainly immune-related side effects as consequence of deregulation of the response of T cells to antigens presented by normal cells [2]. Neurological side effects, such as polyradiculitis, myasthenic syndrome and demyelinating disease of central nervous system (CNS), have been reported [3–6]. In this report, we describe a patient having a radiologically isolated syndrome (RIS), who developed multiple sclerosis (MS) after starting treatment with pembrolizumab therapy for an NSCLC.

A 67-year-old Caucasian female patient was diagnosed with right hilar lung adenocarcinoma EGFR and ALK wild-type PD-L1 positive (>50%), thoracic lymphadenopathy and bone metastases in August 2017. She was a smoker up until 8 years before. During a routine follow-up for cancer staging, the brain MRI scan performed in August 2017 showed multiple T2 white matter lesions, with ovoid morphology and periventricular and infratentorial localization typical for a demyelinating disease, none of them showing contrast-enhancement (Fig. 1). The patient's history was negative for neurological symptoms. In September 2017, the patient started pembrolizumab 200 mg monotherapy every 3 weeks with a subsequent reduction in the size of lung cancer and bone metastases (20 cycles). Ten months after the beginning of treatment with pembrolizumab, in June 2018, the patient developed a subacute right-lower-limb paresis and right-foot paresthesia. A diagnosis of MS according to McDonald criteria 2017 [7] was made after spinal cord MRI revealed a nodular gadolinium enhancing lesion on the dorsal spinal cord and a cervical lesion (Fig. 1), cerebrospinal-fluid-specific oligoclonal bands were detected, and a thorough exclusion of alternative causes was performed. The patient underwent also neurophysiological tests: visual-evoked potentials showed an increase of latency in both eyes after stimulation with check of 30′ and asymmetric latency for right eye > left eye; somatosensory-evoked potentials showed an increased cortical latency for stimulation of both upper and lower limbs. She was treated with methylprednisolone (1 g per day IV for three consecutive days) and the neurological disturbances partially improved, but with persistence of walking limitation. In agreement with the oncologist, the patient is still being treated with pembrolizumab, given the excellent response to cancer treatment, but therapy with interferon (IFN)-β 1a s.c. 3 times a week was added in February 2019 to prevent reactivation of MS. Over the 12 months after MS diagnosis, the patient did not present any new symptoms. Brain and spinal cord MRI examinations performed

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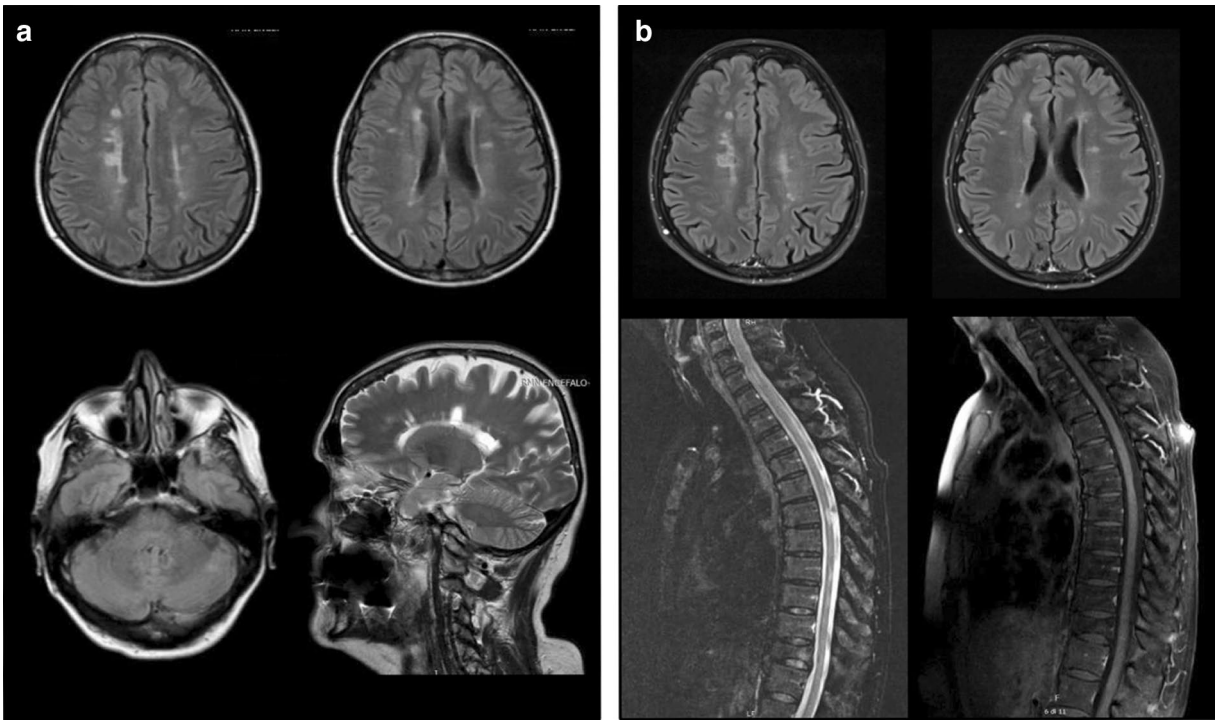

Fig. 1 **a** MRI performed during a routine follow-up for cancer staging (August 2017). Multiple T2 periventricular and infratentorial demyelinating lesions in the brain and in the corpus callosum are visible. **b** The MRI performed in August 2018 after the relapse shows the same demyelinating lesions in the brain and new lesions in the cervical (C5–C6) and dorsal spinal cord (D6)

3 months after the beginning of IFN-β were stable, with a resolution of gadolinium enhancement (Fig. 2).

RIS is characterized by the incidental detection of brain and/or spinal cord lesions compatible with MS by an MRI scan performed for indications other than demyelinating disorders in a patient with no previous neurological manifestations or other clear-cut explanation [7]. In our case, we observed a transition from subclinical RIS to MS, thus it is likely that pembrolizumab triggered disease activity in this patient with subclinical MS. The association between pembrolizumab and MS is not sure but highly probable, because the PD-1/PD-L1 costimulatory pathway plays an important role in modulating disease activity in MS [8]. In fact, in the mouse model for MS (murine experimental autoimmune encephalomyelitis) the block of PD-1 resulted in acceleration of the disease with a dramatical increase in IFN-gamma and tumor necrosis factor (TNF-α) production by T helper (Th)-1 cells in the spinal cord and spleen, and interleukin (IL)-17 production by Th17 cells in the spleen [9]. Finally, cases of MS onset or exacerbation are reported with nivolumab, another anti PD-1 treatment [5, 6].

Patients undergoing treatment with anti-PD-1/PD-L1 therapy should be closely monitored with brain and spinal cord MRI before and during the treatment. In patients with CNS immune syndromes, it would be better, when possible, to choose other treatments for cancer.

We decided to associate a therapy to reduce the risk of MS reactivation, but other cases of association between MS therapy and anti-PD-1 treatment are unknown. After careful evaluation of existing treatments, only IFN-β and natalizumab therapies were considered. However, the treatment with natalizumab was excluded due to high positivity to stratify test and since at that time, data on the beneficial effects of immune-checkpoint inhibitors on progressive multifocal leukoencephalopathy were not yet available [10]. Therefore, the patient started treatment with IFN-β and we are going to evaluate the long-lasting effectiveness of this association in the coming months.

A close collaboration between neurologist and oncologist is essential to early detect any adverse events during the treatment with an immune-checkpoint inhibitor, to optimize their treatment and to define the appropriate time point of cancer treatment discontinuation, if necessary.

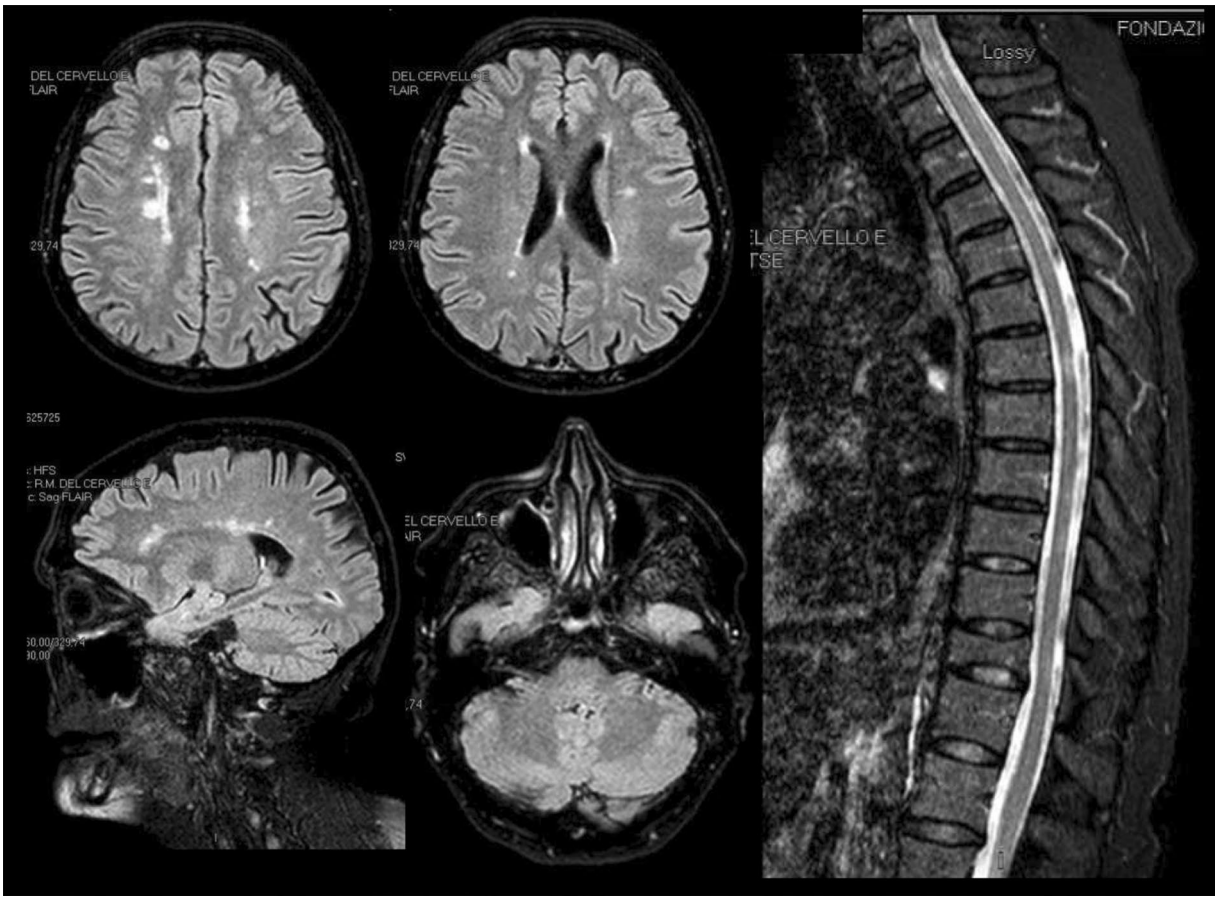

Fig. 2 The brain and spinal cord MRI performed after 2 months of interferon-β therapy (May 2019) shows a stability of demyelinating lesions

Author contributions Conceptualization: MALR; writing—original draft preparation: MALR; acquisition of data: MARL, MAG, LM, GG; interpretation of data: all authors; writing—review, and editing: all authors.

Compliance with ethical standards

Conflicts of interest M. Romeo received honoraria from Sanofi Genzyme, Merck-Serono, and support for traveling from Novartis, Almirall and Teva Pharmaceutical Industries; M. Garassino received personal fees from AstraZeneca, Roche, BMS, MSD; L. Moiola received honoraria from Sanofi Genzyme, TEVA Pharmaceutical Industries, Novartis, Merck-Serono and Biogen Idec; G. Galli report no disclosures; G. Comi received compensation for consulting services and speaking activities from Novartis, Teva Pharmaceutical Industries, Sanofi Genzyme, Merck-Serono, Biogen Idec, Roche, Almirall, Celgene, Forward Pharma, Medday and Excemed; V. Martinelli received honoraria from Sanofi Genzyme, Biogen Idec, TEVA Pharmaceutical Industries, Bayer, Merck-Serono and Novartis; M. Filippi is Editor-in-Chief of the Journal of Neurology; received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Ethical standards A written informed consent was obtained from the patient for the publication of this case.

References

1. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443–2454
2. Reck M, Rodríguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 375:1823–1833
3. Baxi S, Yang A, Gennarelli RL et al (2018) Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 360:k793
4. Fellner A, Makranz C, Lotem M et al (2018) Neurologic complications of immune checkpoint inhibitors. J Neurooncol 137:601–609

5. Garcia CR, Jayswal R, Adams V, Antony LB, Villano JL (2019) Multiple sclerosis outcomes after cancer immunotherapy. Clin Transl Oncol. https://doi.org/10.1007/s12094-019-02060-8
6. Gómez Vicente L, Rubio Viqueira B, De Las Jimenez, Peñas M et al (2016) Relapse in a paucisymptomatic form of multiple sclerosis in a patient treated with nivolumab. Neuro-oncology 18:iv25
7. Thompson AJ, Banwell BL, Barkhof F et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162–173
8. Trabattoni D, Saresella M, Pacei M et al (2009) Costimulatory pathways in multiple sclerosis: distinctive expression of PD-1 and PD-L1 in patients with different patterns of disease. J Immunol 183:4984–4993
9. Takizawa S, Kaneyama T, Tsugane S et al (2014) Role of the Programmed Death-1 (PD-1) pathway in regulation of Theiler's murine encephalomyelitis virus-induced demyelinating disease. J Neuroimmunol 274:78–85
10. Cortese I, Muranski P, Enose-Akahata Y et al (2019) Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. N Engl J Med 380:1597–1605