Clinical Letter

Immune checkpoint inhibitor triggered parkinsonism in a patient with metastatic melanoma

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Dear Editors,

Checkpoint inhibitors (CIs) have revolutionized the treatment of metastatic melanoma (MM). But unbalancing the immune system in many cases results in immune-related adverse events (IRAEs). The spectrum of IRAEs involves the skin, intestine, liver, lungs and endocrine glands, as well as rarer manifestations such as the nervous, cardiovascular and hematopoietic system [1].

Here we report on a patient with MM and a partial response under immune checkpoint inhibitor therapy who developed parkinsonism. The 74-year-old male patient was diagnosed with superficial spreading melanoma with pulmonary metastases in August 2018. Immunotherapy with 1 mg/kg body weight (bw) nivolumab plus 3 mg/kg bw ipilimumab every three weeks was initiated in October 2018.

Both drugs disinhibit T-cell function by inhibiting suppressive "checkpoint" receptors; nivolumab blocks programmed cell death protein 1 (PD-1) and ipilimumab targets the T-lymphocyte-associated antigen 4 (CTLA4) [2, 3].

At the start of treatment, our patient had no concerning neurologic or other symptoms. After the third i.v. injection the patient developed hypophysitis, which was treated with high-dose prednisolone followed by permanent hydrocortisone replacement therapy. Tumor staging after four cycles showed significant regression of pulmonary metastasis, but also a newly diagnosed liver metastasis, which was subsequently treated with transcatheter arterial chemoembolization (TACE). Immunotherapy was switched to monotherapy with 480 mg nivolumab every four weeks in February 2019.

In March 2019 the patient reported movement difficulties that started one month ago for the first time. The following neurological assessment revealed moderate hypokinesia and rigor, as well as dysdiadochokinesia, hypomimia and hypophonia. His gait was unusually slow with a flexed posture and difficulties when turning.

An extensive work-up including brain MRI, EEG and transcranial Doppler ultrasonography did not reveal any cause of these symptoms. Based on the particular combination of symptoms, a moderate idiopathic Parkinson's disease (PD; Hoehn and Yahr stage II) was diagnosed and therapy with the monoamine oxidase inhibitor-B selegiline was initiated. Under this treatment regimen the neurological symptoms significantly improved and are well controlled to date. The absence of other neurological symptoms and the prompt clinical response to selegiline made atypical parkinsonian disorders less likely. Other case-related differential diagnoses that may mimic parkinsonism, but were not present in this patient, are hypothyroidism (after hypophysitis) and hepatic encephalopathy due to liver impairment (after TACE) [4, 5].

Subsequent staging exposed stable disease, and no further systemic cancer treatment was initiated after February 2019 because of the above-mentioned AEs. Due to the coincidence in time between immunotherapy and the onset of parkinsonism we suspected an association between both.

Parkinson's disease (PD) is the most common movement disorder, affecting around 250,000 patients in Germany [6]. It is characterized by specific motor symptoms including hypokinesia, muscle rigor, resting tremor, postural and gait impairment, as well as non-motor symptoms such as constipation or anosmia [7]. Typical pathological findings are degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta and detection of Lewy bodies (cytoplasmic misfolded α-synuclein [α-syn]) aggregating in neuronal cell bodies [8]. The ultimate cause of the degeneration is unknown. Multiple factors such as genetics, abnormal protein processing, oxidative stress, mitochondrial dysfunction or neuroinflammation are considered [8]. Attention has been shifting recently toward autoimmunity as a potential major cause of PD [9].

Current models link infiltrating T-cells with continuous neurodegeneration in the SN [10]. It could be shown that $CD4^+$ and $CD8^+$ T-cells invaded the SN of PD patients and were at significantly greater levels than in non-PD patients [11]. T-cells recognize foreign molecules and sometimes self-peptides in a complex formed with MHC (major histocompatibility complex) molecules. Substantia nigra neurons have been shown to express MHC-I and interact with $CD8^+$ T-cells, contributing to T-cell-mediated cytotoxic attack [12]. In particular, α-syn-specific T-cells are suspected to play a leading role in the initiation and progression of neurodegeneration [10]. It is hypothesized that α-syn-specific $CD4^+$ T-cells activate microglia by recognizing specific peptides complexed with MHC-II on microglia, while $CD8^+$ T-cells target dopaminergic neurons that present a specific epitope bound to MHC-I [10].

We speculate that in the present case, onset of parkinsonism is triggered by therapy with nivolumab and ipilimumab, which basically enhances T-cell activation by targeting coinhibitory molecules such as CTLA-4 or PD-1 (which physiologically attenuate T-cell activation mediated by MHC-antigen T-cell receptor interaction) [2, 3].

As in other IRAEs, we believe that there may be a short timeframe for adequate immunosuppression to prevent irreversible loss of cells ("burned out" phase). We therefore suggest that with checkpoint inhibitor therapy, there should be careful consideration of early treatment with high-dose intravenous steroids or plasmapheresis soon after development of parkinsonism.

It is still unclear whether checkpoint inhibitor therapy in this case only facilitated the onset of PD, or might have also caused parkinsonism in a non-PD predisposed patient. This is particularly interesting since melanoma patients have an increased risk of contracting PD. The mechanistic link between both diseases may be α-syn, which exerts toxic functions in PD, but promotes cancer cell survival in MM [13].

So far only one case of parkinsonoid syndrome manifesting during therapy with pembrolizumab has been reported in a melanoma patient, but in this case, there is unfortunately no detailed report on the patient's history and course of neurological symptoms [1].

In summary, the present case suggests that unexpected and rare symptoms presenting during or after checkpoint inhibitor therapy should be considered as potentially drug-associated, since any organ system may be affected. In future, a multidisciplinary approach may be the only way to effectively combat the versality of potential IRAEs.

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Conflict of interest

None.

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