

PD-1 Antibody-induced Guillain-Barré Syndrome in a Patient with Metastatic Melanoma

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Guillain-Barré syndrome (GBS) presents as acute inflammatory demyelinating polyneuropathy, which leads to rapid-onset muscle weakness classically caused by immune-mediated damage to the peripheral nervous system.

We report here a case of GBS occurring during treatment with nivolumab. Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its 2 known programmed death ligands, PD-L1 and PD-L2. Nivolumab can thereby restore anticancer immune responses by abrogating PD-1 pathway-mediated T-cell inhibition (1). In addition, we discuss possible underlying disease mechanisms and treatment options.

CASE REPORT

A 51-year-old man was diagnosed with nodular melanoma with a tumour thickness of 2 mm on the right cheek and 2 positive cervical sentinel lymph nodes. After a neck dissection revealing one additional metastatic lymph node he received adjuvant treatment with high-dose intravenous interferon (IFN)- α 2b (20 mU/m²/day for 1 month, followed by 10 mU/m² 3 times/week subcutaneously). After 6 months treatment was discontinued because a submental lymph node metastasis occurred on the right side, which was excised. Two months later the patient developed distant metastases in the lung and liver (Fig. S1a¹), the latter being histologically confirmed by a liver biopsy. The BRAF, NRAS and C-kit mutation status were wild-type. We included the patient in a double-blind, randomized phase III study in which nivolumab was tested against dacarbazine. Staging procedures after 3 months of treatment showed “stable disease” (Fig. S1b¹) with a decrease in the sum of target lesions of 30% (RECIST 1.1) and treatment was continued. While on treatment, S100 and LDH decreased from the initial 0.833 to 0.057 μ g/l, and from 279 to 194 U/l, respectively.

Five months after initiation of study medication the patient reported muscular weakness in both legs and peripheral paraesthesias. Besides the study medication the patient received levothyroxine (175 μ g/once daily)

and metoprolol (100 mg/once daily). Neurological examination revealed formication in both hands, bilateral hypaesthesia of the legs up to the upper thigh, bilateral muscular weakness, and absent tendon reflexes in both legs. The patient was afebrile; there were no clinical findings indicating infectious causes. Hepatitis A, B, and C and HIV were ruled out by repeated negative blood tests. The patient's history concerning recent travel activities, vaccinations, or insect bites was negative. The patient was hospitalized and magnetic resonance imaging of the brain and the spinal cord were unremarkable. In addition, there were no pathological findings in serum auto-antibodies, including ganglioside M1 (GM1)-, ganglioside Q1b (GQ1b)-, and myelin-associated glycoprotein (MAG)-antibodies. Further blood tests revealed neither active viral infections (Epstein-Barr virus, cytomegalovirus, hepatitis A, B, and C and HIV) nor any auto-immune related abnormalities (antinuclear antibody, extractable nuclear antigens, anti-neutrophil cytoplasmic antibody, anti-DS DNA). Cerebrospinal fluid (CSF) analysis showed an elevated protein level of 0.73 g/l (normal range <0.4 g/l). Electroneurography (ENG) was diagnostic for an acute demyelinating sensorimotor polyneuropathy. These pathological findings were consistent with diagnosis of GBS (Fig. S2a, b¹) and were rated as adverse event grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE). The patient was unblinded and found to have received nivolumab treatment (3 mg/kg bodyweight i.v. every 2 weeks). Treatment with intravenous immunoglobulin (IVIG) (0.4 g/kg bodyweight) for 5 days was initiated by Department of Neurology, as usual first choice in GBS, but did not lead to any clinical improvement. Hence, after consultation with the dermatologists and literature research a systemic corticosteroid therapy (methylprednisolone, 1 mg/kg bodyweight) was started. Clinical recovery started 48 h later and was nearly complete after 6 weeks, as confirmed by ENG (normal F wave latency, no A waves, normal distal motor latency, no temporal dispersion). Corticosteroids were tapered and then stopped after 8 weeks. ENG results suggested a stable remission 5 and 12 months after the initial examination for GBS (Fig. S2c, d¹). Nivolumab was permanently discontinued and a partial response was documented, which, one year after initiation of nivolumab treatment, is still ongoing. To date, no other anti-tumoural treatment has been initiated.

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DISCUSSION

PD-1 is expressed on activated T cells, but also on regulatory T cells (Treg), natural killer cells, and activated B cells (2). Nivolumab was recently compared with dacarbazine in a phase III randomized double-blind study in patients with treatment-naïve BRAF wild-type advanced melanoma, in which our patient was included (1). The overall survival rate at one year was 72.9% in the nivolumab group and 42.1% in the dacarbazine group.

It is known that PD-1 antibodies also can cause severe immune-related adverse events (irAE) but these appear significantly lower than with ipilimumab (3). Recently, Zimmer et al. (4) have summarized very rare side-effects affecting the nervous system, respiratory tract, musculoskeletal system, heart, blood and eyes, such as meningo-(radiculitis), polyradiculitis, cardiac arrhythmia, asystolia, and paresis. Cutaneous side-effects are rare, but lichenoid reactions and psoriasis exacerbation have been reported (5, 6).

It is known that viral infections, such as EBV, CMV, hepatitis A, B, and C, HIV, and the currently much-discussed Zika virus, can be potential causes of GBS, which in our case were ruled out by negative blood tests and past medical history.

Studies of GBS showed increased levels of ganglioside-directed T lymphocytes (7). Therefore, T-cell activation and proliferation caused through PD-1 antibodies probably play a role in the pathogenesis of nivolumab-induced GBS. GBS may be caused by PD-1 blockade on peripheral lymphocytes that become refractory to the inhibitory effects of Treg.

It is assumed that aberrant humoral immunity is being involved in the pathogenesis of GBS, including anti-ganglioside antibody production (8). This hypothesis is based on detection of deposition of immunoglobulin G and complement activation products on the axolemma of motor fibres and the presence of myelin-specific plasmablasts and B cell expansion in an animal model of GBS, and depletion of these cells. In a fraction of patients with GBS anti-ganglioside antibodies can be found. In contrast, neither patients with reported ipilimumab-induced GBS nor our patient with PD-1 antibody-induced GBS showed detectable anti-ganglioside antibodies (9, 10).

PD-1 to PD-L1 engagement physiologically suppresses self-reactive T cells to preserve self-tolerance and protect against autoimmune pathology within the CNS (11, 12). T-cell-mediated autoimmunity against melanoma cell antigens may also affect myelin antigens on the Schwann cell membrane as a result of cross-reactivity due to a molecular mimicry. Melanocytes and Schwann cells originate from the neural crest and share many epitopes for humoral and cellular immune responses.

Others have hypothesized that T cells with deficient PD-1 signalling may be preferentially polarized towards effector T-cell differentiation, and that the expression of PD-1 and inducible T-cell co-stimulator (ICOS) may de-

termine the immunological status of circulating memory T follicular helper (Tfh) cells in patients with GBS (8).

Rare cases of IFN-induced inflammatory demyelinating polyneuropathy have been described in the literature (13). An influence of pretreatment with IFN in our patient cannot be fully excluded. However, no symptoms occurred during the 6 months of IFN treatment and in the 2 months after stopping of IFN and before the start of the PD-1 antibody. Hence, IFN is not very likely to have caused the GBS.

Of note, ipilimumab-induced GBS has been reported to respond to high-dose intravenous-corticosteroid therapy. This is consistent with the observation in our patient, who did not respond to earlier intravenous immunoglobulin application, which is considered first-line treatment in classical cases of GBS of infectious causes (9).

In conclusion, this report of GBS in a nivolumab-treated patient underlines the importance of correctly identifying first neurological symptoms, and demonstrates the effectiveness of treatment with systemic corticosteroids.

The authors declare no conflicts of interest.

REFERENCES

1. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; 372: 320–330.
2. Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med* 2009; 206: 3015–3029.
3. Johnson DB, Peng C, Sosman JA. Nivolumab in melanoma: latest evidence and clinical potential. *Ther Adv Med Oncol* 2015; 7: 97–106.
4. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016; 60: 210–225.
5. Komori T, Honda T, Irie H, Otsuka A, Kabashima K. Lichen planus in irradiated skin during nivolumab treatment. *Acta Derm Venereol* 2017; 97: 391–392.
6. Matsumura N, Ohtsuka M, Kikuchi N, Yamamoto T. Exacerbation of psoriasis during nivolumab therapy for Metastatic Melanoma. *Acta Derm Venereol* 2016;96: 259–260.
7. Bot I, Blank CU, Boogerd W, Brandsma D. Neurological immune-related adverse events of ipilimumab. *Pract Neurol* 2013; 13: 278–280.
8. Che Y, Qiu J, Jin T, Yin F, Li M, Jiang Y. Circulating memory T follicular helper subsets, Tfh2 and Tfh17, participate in the pathogenesis of Guillain-Barré syndrome. *Sci Rep* 2016; 6: 20963.
9. Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barre syndrome in a melanoma patient. *Ann Oncol* 2011; 22: 991–993.
10. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. *Neuro Oncol* 2014; 16: 589–593.
11. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; 12: 252–264.
12. Metcalfe W, Anderson J, Trinh V, Hwu WJ. Anti-programmed cell death-1 (PD-1) monoclonal antibodies in treating advanced melanoma. *Discov Med* 2015; 19: 393–401.
13. Lin W, Harding HP, Ron D, Popko B. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. *J Cell Biol* 2005; 169: 603–612.