Anti-CTLA-4 antibody-induced Guillain–Barré syndrome in a melanoma patient

A 57-year-old woman was diagnosed with a macroscopic axillary lymph node metastasis of a primary occult melanoma for which she underwent a complete axillary lymph node dissection. Three years later, recurrence was diagnosed when an intra-abdominal metastasis inferior to the spleen became apparent. Progression of this metastasis was documented despite first-line chemotherapy with dacarbazine (three cycles) and second-line chemotherapy with carboplatinum and paclitaxel (two cycles). During second-line chemotherapy, she had developed severe anorexia, fatigue and depression (for which treatment with venlafaxine had been initiated). There had been no signs or symptoms of paclitaxel-induced neurotoxicity. When she first consulted our melanoma clinic, alimentation was maintained by feeding through a nasogastric tube and her Karnofsky performance status was 50%. Following partial recovery of her general condition, the patient initiated monotherapy with ipilimumab (Bristol-Myers Squibb Co., New York, NY) in July 2010. Ipilimumab, an IgG1 mAb against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), was administered at a dose of 3 mg/kg of body weight given i.v. every 3 weeks. One week after the third dose of ipilimumab, the patient reported over telephone that she had started experiencing dysesthesia (numbness and tingling) at the hands and feet. Within 48 h thereafter, she devolved a rapidly ascending loss of sensory and motor function of the limbs. At the time of admittance to the emergency department, she had lost the capacity to walk without support as well as a sensory loss that had progressively ascended to the level of the knees and elbows. Further clinical neurological examination revealed a loss of the deep tendon reflexes; there were no signs of meningism or cranial nerve impairment. She had preserved a normal consciousness and was apyretic; there were no findings indicating infection or progression of her melanoma. Laboratory findings on venous blood were unremarkable; magnetic resonance imaging of neither the brain nor the spinal cord revealed any abnormalities. Electromyography (EMG) was diagnostic for a generalized motor and sensory demyelinating polyneuropathy. Cerebrospinal fluid (CSF) analysis showed clear appearance with a normal glucose (105 mg/dl), slightly elevated lactate (2.5 mmol/l; normal < 1.7), <2/mm³ nucleated cells, <2/mm³ red blood cells but an elevated protein level (total protein 167 mg/dl (normal range: 29–67), albumin 96.6 mg/dl (normal range: 14–20), with elevated IgG (8.05 mg/dl; normal range: 1.7–3.4) with the presence of oligoclonal bands in CSF and serum. Microbiological culture remained negative as well as PCR for Borrelia burgdorferi. These pathological findings are consistent with a diagnosis of the Guillain–Barré syndrome.
GBS; a form of potentially reversible acute demyelinating polyneuropathy). Upon initiation of treatment with high-dose corticotherapy (40 mg of methylprednisolone administered i.v. two times per day), there was no further aggravation of symptoms. Clinical recovery started 48 h later and was nearly complete after 4 weeks (confirmed by EMG 2.5 months after the initial examination). Corticosteroids were tapered and stopped after 18 weeks. Ipilimumab was permanently discontinued. Twelve and twenty-four weeks after the initiation of ipilimumab, tumor evaluation by 18F-FDG (2-[fluorine-18]fluoro-2-deoxy-D-glucose)–positron emission tomography/computed tomography indicated a loss of 18F-FDG uptake and regression of the longest diameter of the metastasis by 20% and 30%, respectively (Figure 1).

Ipilimumab is a new therapeutic monoclonal antibody with immunomodulatory activity that improves the overall survival in patients with pretreated melanoma [1, 2]. The exact mechanism of tumor regression related to this CTLA-4-blocking mAb has not been revealed completely. Immune activation in patients treated with ipilimumab is evident from increased CD4(+) and CD4(+) human leukocyte antigen-DR(+) T-lymphocyte and interferon-γ-producing CD4(+)ICOShi counts in the circulation. Furthermore, regressing melanoma metastases are characterized by infiltration of CD8-positive T cells. Patients treated with ipilimumab are at risk for immune-related adverse events (irAE) at the level of the skin, digestive tract, liver and endocrine organs [3]. Early diagnosis followed by immunosuppressive treatment and discontinuation of ipilimumab results in recovery from irAE in the vast majority of cases [3]. The incidence of irAE involving the central or peripheral nervous system has been very rare in patients treated with ipilimumab in phase II/III clinical trials [1, 2, 4, 5]. To our knowledge, this is the first report of ipilimumab-related GBS. A recently reported case report of inflammatory enteric neuropathy may however represent another related manifestation of ipilimumab-triggered neurotoxicity. Predisposing factors for the development of the GBS in patients treated with ipilimumab are not evident and other immunotherapeutic antibodies with a different mode of action have been associated with the GBS as well. Antibodies directed against cell surface gangliosides expressed in human peripheral nerve axolemma have been related to the pathophysiology of the GBS. Immune activation by ipilimumab may cause the GBS by braking peripheral tolerance to such ganglioside-related epitopes in patients with preexisting humoral autoimmunity against them. In part, this could be mediated by the effect of CTLA-4 blockade on the resistance of peripheral lymphocytes to the inhibitory effects of regulatory T cells (Treg). One may speculate that prior therapy with neurototoxic chemotherapy could predispose patients for ipilimumab-related GBS by triggering humoral autoimmunity to ganglioside antigens through mechanisms of antigen retrieval. Because of the increasing use of anti-CTLA-4 antibodies in the treatment of melanoma and other malignancies, clinicians should be aware of this rare but potentially life-threatening irAE. While high-dose i.v. immunoglobulins or plasmapheresis is the recommended therapeutic option for classical GBS, our patient readily responded to high-dose i.v. corticotherapy, a treatment that is considered nonactive in the classical presentation of GBS.

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disclosure
BN is a paid consultant for Bristol-Myers Squibb. SW has no conflict of interest.

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doi:10.1093/annonc/mdr028
Published online 28 February 2011