Motor polyradiculopathy during pembrolizumab treatment of metastatic melanoma

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

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Abstract

Introduction: Pembrolizumab, a monoclonal antibody directed against the immune checkpoint PD-1 (programmed cell death-1 receptor), has improved survival in patients with advanced melanoma. Neuromuscular immune-mediated side effects have been rarely reported.

Methods: We describe a 44-year-old man with metastatic melanoma who presented with progressive muscle weakness after 23 doses of pembrolizumab.

Results: The patient developed asymmetric, proximal muscle weakness and atrophy in all four limbs. Cerebrospinal fluid examination showed albuminocytologic dissociation. MRI revealed contrast enhancement of the lumbosacral roots. Electrodiagnostic studies demonstrated widespread fibrillation potentials in all four limbs, suggesting a generalized motor polyradiculopathy. Despite pembrolizumab discontinuation and treatment with steroids and intravenous immunoglobulin, limb weakness worsened. Electrodiagnostic studies were repeated, and showed marked and diffuse axonal motor damage. Seven weeks after clinical onset the patient was treated with plasma exchanges. He showed no further deterioration.

Discussion: We report a severe motor polyradiculopathy associated with an anti-PD-1 agent that expands the spectrum of neuromuscular complications of this class of drugs.

Key words: immune neuropathy, pembrolizumab, toxic neuropathy, polyradiculoneuropathy, anti-programmed death-1 receptor

Introduction

Pembrolizumab is a humanized monoclonal antibody directed against the programmed cell death-1 receptor (PD-1)[1], a T-cell immunoinhibitory checkpoint protein. It has emerged recently as a promising immune-based therapy for the treatment of metastatic melanoma[2], advanced non-small cell lung cancer[3], and other malignancies. Pembrolizumab acts by releasing PD-1 from its ligand and restoring an immune response to eliminate tumor cells[1]. Due to this mechanism of action, some immune-related side effects have been reported, mainly affecting the skin, gastrointestinal tract, liver and endocrine system[4, 5]. The description of neurological adverse events has been rare. We report a patient who developed severe motor polyradiculopathy during pembrolizumab treatment of metastatic melanoma.

Case Report

A 44-year-old man was diagnosed with a 2.2-mm Breslow, Clark IV, non-ulcerated melanoma on the right leg in 2010. Wide local excision and sentinel lymph node biopsy were negative. He received high dose alpha-interferon for 12 months. In April 2012, a solitary right lung nodule was resected and pathology was consistent with metastatic melanoma (molecular testing negative for BRAF mutation). A chest computed tomography (CT) in January-2013 revealed new bilateral subcentimeter lung metastases, which progressed 10 months later. At that point, the patient was enrolled into a randomized phase III clinical trial comparing two schedules of pembrolizumab with ipilimumab for metastatic melanoma (NCT01866319). He was allocated to receive treatment with pembrolizumab 10 mg/Kg every 2 weeks. The treatment was well tolerated, producing only mild asthenia as an adverse effect. The patient experienced a partial response (76% reduction), according to RECIST 1.1 criteria[6] on the first CT

assessment at 3 months, which was sustained over the following months. After the 23th dose (week 46) elevated liver enzymes [aspartate transaminase 75 U/l (normal range 5-40), alanine transaminase 252 U/l (normal range 5-40), gamma-glutamyl transferase 119 U/l (normal range 5-40)] were detected in a routine blood test; pembrolizumab infusion was delayed and treatment with oral prednisone (1mg/kg/day) was started.

One week later, the patient developed progressive proximal limb weakness, mainly involving the left arm and the right leg. The muscle weakness worsened over the ensuing eight weeks. Neurological examination three weeks after the onset of symptoms revealed significant atrophy of the left supraspinatus, infraspinatus, deltoid and biceps brachii muscles (Figure 1), and of the right quadriceps muscle, without fasciculations. There was weakness of left arm abduction and right hip flexion. Deep tendon reflexes were absent in the left arm and both legs and hypoactive in the right arm. Sensory exam was normal. Nerve conduction studies showed normal sensory and motor conduction velocities and amplitudes, bilaterally in median, ulnar, tibial, peroneal and sural nerves, with normal F-wave latencies (Table 1). We did not find conduction blocks or temporal dispersion of compound muscle action potentials (CMAPs). Needle electrode examination detected fibrillation potentials in left biceps brachii muscle and reduction in the number of active motor unit potentials in left biceps brachii, left deltoid, and right tibialis anterior muscles. Cerebrospinal fluid (CSF) analysis demonstrated albuminocytologic dissociation, with an increased protein level (67 mg/dl, normal range 15-45) and no cells. Atypical cells were not detected in 2 lumbar punctures. A spinal magnetic resonance image (MRI) showed diffuse and homogeneous contrast enhancement of the ventral lumbosacral roots (Figure 2, A-B). Brain MRI was normal, and laboratory tests for anti-nuclear antibodies, Lyme titers, human immunodeficiency virus, cytomegalovirus, Epstein-Barr and B, C and E hepatitis viruses were normal or

negative. The study of porphyrins in the urine was normal and serum testing for anti-ganglioside and onconeuronal antibodies (anti-Hu, Yo, Ri, CV2, Ma2, Amphiphysin, Tr, ZIC, SOX1) was negative.

The suspected diagnosis was acute motor polyradiculopathy with a diffuse and asymmetric distribution, probably immune-mediated, and pembrolizumab was discontinued. The coexistence of elevated liver enzymes which was related to pembrolizumab, supported the presumably immune-mediated mechanism. Five weeks after symptom onset infusions with intravenous immunoglobulin (0.4 g/kg for 5 days) were started and oral prednisone was maintained. Over the following weeks, the patient experienced gradual worsening of his quadriparesis, involving distal muscles, especially of the upper limbs, with atrophy of the dorsal interosseous muscles bilaterally. Sensory examination was normal, plantars were downgoing, and there was no cranial nerve involvement or signs of dysautonomia. He demonstrated a steppage gait, and ambulation was only possible with assistance. A second EMG (Table 1) performed 5 weeks after the onset of weakness, showed marked reduction in the CMAP amplitude of the motor nerves with normal conduction velocities, absent or minimally prolonged F-wave latencies and severe active denervation in all muscle groups studied, suggesting diffuse axonal motor damage. The patient was treated with plasma exchange (6 sessions) seven weeks after the onset, and prednisone was progressively tapered over a period of two months. At eight weeks from symptoms onset, neurological symptoms stabilized; he was discharged from the hospital and started intensive rehabilitation. He demonstrated a gradual improvement, especially in proximal muscle strength of his left arm and right leg. At the last follow-up visit, twelve months after symptom onset, muscle strength of the left biceps brachii and interossi of both hands was 3/5, right quadriceps 3/5, and tibialis anterior of both legs 0/5 by the MRC scale. Persistent

although less pronounced atrophy of shoulder girdle, interosseous and quadriceps muscles was present, with generalized areflexia. He required support for ambulation and used ankle foot orthoses. The minimal improvement in strength in the arms allowed him to use a computer but he was unable to resume most of his usual daily activities. A 1 year follow-up spinal MRI revealed no contrast enhancement in the lumbar nerve roots (Figure 2, C-D). A third and fourth EMG showed active and chronic denervation without signs of demyelination or sensory involvement in the affected territories (Table 1). The patient did not receive further anticancer or immunosuppressive agents and had stable residual metastatic disease until 16 months after the last dose of pembrolizumab, when enlargement of metastatic lung nodules was detected and managed surgically.

Discussion

Recently, immune-based therapies (IBT) such as ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), and pembrolizumab and nivolumab, both anti-PD-1 agents, have significantly improved survival in patients with advanced melanoma. Immune-related adverse events involving the central or peripheral nervous system associated with IBT were very rare in phase II and III clinical trials, but since approval, occasional neurological side-effects of varying severity have been reported. Here, we report the case of a motor polyradiculopathy associated with anti-PD-1 treatment.

Manousakis et al[7] reported a patient who after three doses of ipilimumab developed a monophasic multifocal radiculoneuropathy, without evidence of demyelination in neurophysiological studies (no temporal dispersion, normal conduction velocities and progressive loss of CMAP and SNAP amplitudes involving nerves of all four limbs in subsequent studies). A sural biopsy supported the absence of demyelination (normal number of myelinated axons), but in that case, the clinical onset

was acute, evolving along 3-4 weeks, with cranial nerve, sensory and motor involvement, and the patient demonstrated better clinical recovery than ours. Other cases of neuropathy have been reported related to ipilimumab, mostly monophasic demyelinating polyradiculoneuropathies with sensory-motor involvement[8-10]. One patient had severe involvement of the myenteric plexus as the initial manifestation[11] and another patient had concomitant meningitis (meningo-radiculo-neuritis) [12]. Recently, two patients who received pembrolizumab developed a chronic demyelinating polyradiculoneuropathy and Guillain-Barré syndrome (GBS) [13]. One patient has been diagnosed with GBS after receiving pembrolizumab and dabrafenib[14]. Cases of myasthenia gravis or exacerbation of a preexisting myasthenia gravis in relation to ipilimumab but also with pembrolizumab and nivolumab[15-17] and necrotic myositis[18] have been also reported.

Finally, the spectrum of neurological complications associated with the administration of IBT has included aseptic meningoencephalitis[19],inflammatory demyelinating lesions in brain or spinal cord[8,20,21], worsening of multiple sclerosis [22], conversion to definite multiple sclerosis from a radiologically isolated syndrome[23] and encephalitis with presence of anti-NMDAR antibodies or seronegative[24,25].

Usually, the peripheral nerve involvement associated with melanoma is due to direct spread of malignant cells, which was also suspected given the presence of contrast enhancement of the lumbosacral roots. However, in our patient serial CSF cytology studies were negative, the neurological symptoms stabilized after immunomodulatory treatment, and a follow-up MRI no longer showed contrast enhancement in the nerve roots, ruling out leptomeningeal disease. A progressive lower motor neuron syndrome was also initially considered, but the presence of enhancing lumbar roots and albuminocytologic dissociation in the CSF were more suggestive of

primary involvement of the nerve rather than the neuronal cell body. Acute motor axonal neuropathy (AMAN) represents a variant of GBS, with axonal motor damage in the absence of signs of demyelination. Patients with AMAN have longer time to recovery and poorer functional outcome than those with GBS[26]. In our patient, the symptoms were purely motor but the presentation was subacute, evolving along eight weeks. An extensive work-up ruled-out other causes of subacute/chronic neuropathy (infectious, paraneoplastic, porphyria). The absence of pain and the distal symmetric involvement of upper and lower limb muscles made neuralgic amyotrophy less likely. A variant of diabetic lumbosacral radiculoplexus neuropathy (DLRPN) has been described recently in a series of patients[27] that was characterized by a painless and a more symmetrical distribution than the common form of DLRPN. Although our patient was not diabetic (fasting glucose values < 126 mg/dL in all the assessments), we can not exclude this syndrome as a possible explanation.

In general, polyradiculopathies described in association with the use of immune checkpoint inhibitors have shown good outcomes, with improvement of most of the neurological deficits and in some cases full recovery of function[10, 12]. The initial therapeutic approach in the majority of these neuropathies has been the cessation of the IBT and the administration of intravenous steroids, although, in most of the cases steroids alone have been ineffective to stop the acute neurological worsening and have been followed by plasma exchange or intravenous immunoglobulin. Whether the clinical recovery or the stabilization of symptoms is a consequence of the treatments received or reflects the natural evolution of the neuropathy is unclear.

The mechanism by which pembrolizumab may produce peripheral nerve injury is not well known. Effective antitumor response is induced by blocking the negative regulators of T-cell function that exist both on immune cells and on tumor cells. PD-1 is

expressed by T-cells after being exposed to an antigen for a long period of time, and PD-L1 (the ligand) is expressed on the tumor cells. Blocking either of them can restore a pre-existing immune response mediated by T cells in the tumor microenviroment. In fact, immune-mediated disorders occurred in PD-1 knockout mice and clinical trials with anti-PD1 agents excluded patients with autoimmune diseases or medical conditions that required immunosuppression[2, 28]. Neurological toxicity may be mediated in part by T-cell infiltration or inflammatory cytokines released by activated cells. In clinical studies, immunohistochemistry of affected skin and gut revealed infiltration by CD4 and CD8 T cells and increased serum inflammatory cytokines[8, 10]. The sural nerve biopsy of a patient with multifocal radiculoneuropathy receiving ipilimumab showed endoneurial perivascular inflammatory infiltrates of T cells and histiocytes[6]. Findings such as high white blood cell count (lymphocyte predominance) in the lumbar puncture may point to an immune-mediated etiology[11]. Another mechanism hypothesized in a case of GBS is that the immune activation by ipilimumab inhibits peripheral tolerance to ganglioside-related epitopes in patients with preexisting humoral autoimmunity (ie. prior chemotherapy) through antigen retrieval[9]. However, in our case, an elevated lymphocyte count was not found in the CSF, serum anti-ganglioside antibodies were not detected and we did not consider performing a biopsy given that our patient had pure motor involvement.

In conclusion, treatment with pembrolizumab can be associated with distinctive inflammatory adverse effects. As its clinical use is expanding rapidly, early recognition and management of related adverse events are essential to prevent patient morbidity and mortality. This is particularly true in view of our patient's limited response to immunosuppressive treatment and poor functional outcome.

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Abbreviations List

AMAN: acute motor axonal neuropathy

CMAP: compound muscle action potential

CSF: cerebrospinal fluid

CT: computed tomography

CTLA-4: cytotoxic T-lymphocyte 4

EMG: electromyography

GBS: Guillain-Barré syndrome

IBT: immune-based therapies

MRC: medical research council

MRI: magnetic resonance image

NCS: nerve conduction studies

NMDAR : N-methyl-D-aspartate receptor

PD-1: programmed death-1 receptor

PD-L1: programmed death ligand-1

SNAP: sensory nerve action potential

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Table 1. Nerve conduction studies

	Time-point (days after symptom onset)				
	10 days	36 days	86 days	395 days	Cutt-off normal values
Nerve Conduction Studies					
Median nerve					
Motor distal latency	3.1	3.4	NR	3.7	≤3.9
CMAP amplitude	15	7	NR	13.7	≥6.0
Motor CV	53	48	NR	41.5	≥50.0
SNAP Amplitude	ND	ND	17	26	≥21
F-wave latency	29	32	NR	30	≤31
Peroneal nerve					
Motor distal latency	3.9	5.6	NR	4.7	≤5.0
CMAP amplitude	4	1	NR	0.1	≥2.0
Motor CV	49	46	NR	53.7	≥42.0
F-wave latency	52	59	58	54	≤57.0
Tibial Posterior nerve					
Motor distal latency	6.9	8.7	7.4	6.8	≤6.0
CMAP amplitude	3.5	2	2	2.6	≥3.0
Motor CV	52	43	48	42.8	≥38.0
F-wave latency	54	60	59	54	≤57.0
Sural Nerve					
Distal latency	2.8	3.1	2.7	2.2	≤3.0
SNAP amplitude	10	6.4	6.3	12.5	≥5.0
Sensory CV	50	49.2	50.7	55.3	≥38.0

Needle examination					
Upper limbs					
Biceps Brachii					
Fibrillation potentials	++	++	+++	+	-
MUP recruitment	Reduced	Reduced	Reduced	Reduced	-
Deltoid					
Fibrillation potentials	None	++	+++	+	-
MUP recruitment	Reduced	Normal	Reduced	Normal	-
Lower limbs					
Tibialis Anterior					
Fibrillation potentials	None	++	+++	+	-
MUP recruitment	Reduced	Reduced	Reduced	Reduced	-
Quadriceps					
Fibrillation potentials	ND	++	+++	ND	-
MUP recruitment	ND	Reduced	Reduced	ND	-
Transcranial magnetic stimulation					
First interosseous MEP	22	ND	25	21	≤23
Tibialis Anterior MEP	33	ND	NR	NR	≤35

CMAP, compound muscle action potential (in millivolts), CV, conduction velocity (in meter/second); MEP, motor evoked potential (in milliseconds); SNAP, sensory nerve action potential (in microvolts), ND, not done, NR, no response; Fibrillation qualitative measurement: + minimum; ++ mild; +++ moderate; ++++ severe.

Figure 1. Left shoulder girdle muscle atrophy 3 weeks after symptoms onset.

Figure 2. Lumbar spine MRI: Sagittal (A) and axial (B) T1 post-contrast image showed diffuse and homogeneous contrast enhancement of the ventral lumbosacral roots (arrows), which disappeared in the MRI performed 12 months later (C and D).

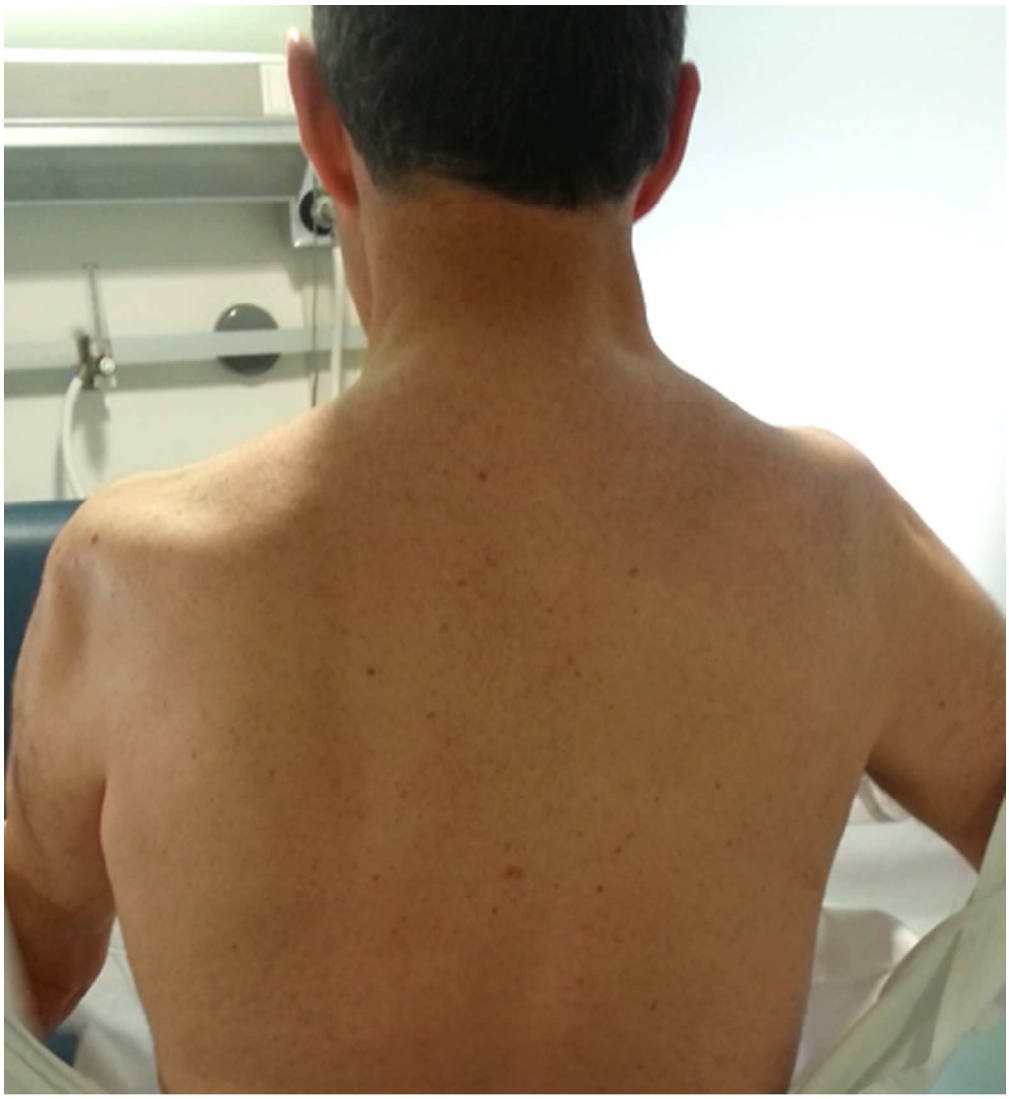

Figure 1

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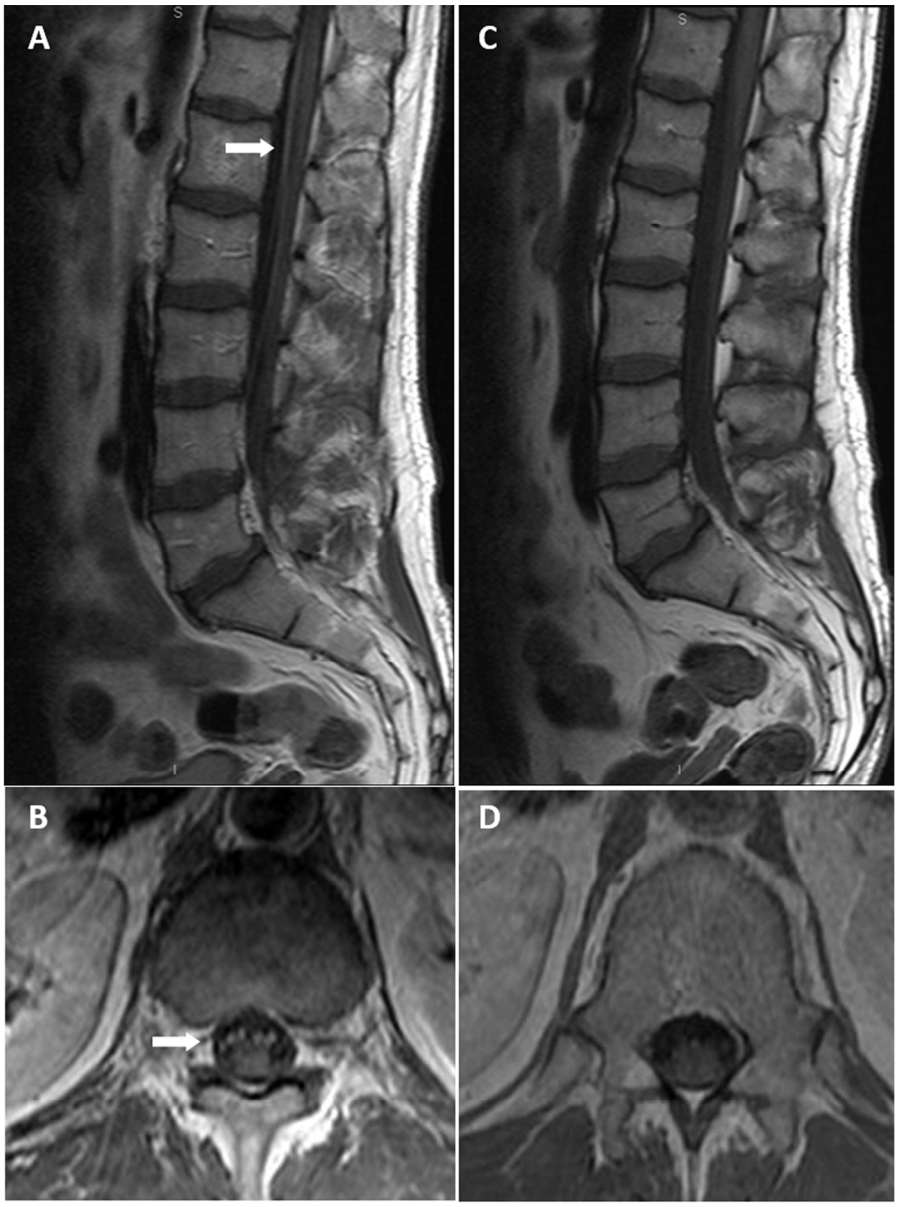

Figure 2

129x173mm (300 x 300 DPI)