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Letter to Editor Open Access

Acute Demyelinating Polyneuropathy Caused by Nivolumab in a Man with Metastatic Non-Small Cell Lung Cancer

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Immune checkpoint inhibitors include programmed cell death-1 (PD-1) receptor inhibitors, programmed cell death ligand-1 (PDL-1) inhibitors and Cytotoxic T-Lymphocyte Associated molecule 4 (CTLA-4) inhibitors and are novel treatment against certain cancers like non-small cell lung cancer (NSCLC), melanoma and renal cell cancer. They act by boosting immune response against cancer cells and have improved prognosis of patients with these cancers significantly shifting the treatment paradigm. Despite their clinical benefit, these agents are associated with the development of immune-related adverse events (IRAEs) [1] associated with significant morbidity. Immune checkpoint inhibitors such as Ipilimumab and Nivolumab are known to cause immune-mediated acute demyelinating polyneuropathy [2,3]. We hereby report a case of a man with acute demyelinating neuropathy associated with Nivolumab that was treated successfully with high dose intravenous methylprednisolone (IVMP).

Site	NR	Peak (ms)	P-T Amp (μV)	Onset (ms)	O-P Amp (μV)	Site 1	Site 2	Delta-0 (ms)	Dist (cm)	Vel (m/s)
Right Ulnar Dig V Anti-Sensory (Digit V-14 cm)										
Wrist		3.0	6.0	2.1	4.1	Wrist	Digit V-14 cm	2.1	13.0	62
Left Sural Anti-Sensory (Lat Mall)										
Calf	NR					Calf	Lat Mall		14.0	
Right Sural Anti-Sensory (Lat Mall)										
Calf	NR					Calf	Lat Mall		14.0	

Table 1a: Anti-sensory summary table.

Site	NR	Onset (ms)	O-P Amp (mV)	Site 1	Site 2	Delta-0 (ms)	Distance (cm)	Velocity (m/s)
Right Peroneal Motor (Ext Dig Brev)								
Ankle		5.2	0.5	B Fib	Ankle	8.4	30.0	36
B Fib		13.6	0.3	Poplt	B Fib	2.3	9.0	39
Poplt		15.9	0.3					
Left Tibial Motor (Abd Hall Brev)								
Ankle		6.0	0.3	Knee	Ankle	16.3	41.0	25
Knee		22.3	0.2					
Right Tibial Motor (Abd Hall Brev)								
Ankle		6.5	0.4	Knee	Ankle	13.6	41.0	30
Knee		20.1	0.3					
Right Ulnar Nerve (Abd Dig Minimi)								
Wrist		3.1	10.1	B Elbow	Wrist	4.5	23.0	51

B Elbow		7.6	7.4	A Elbow	B Elbow	3.3	18.0	55
A Elbow		10.9	7.5					

Table 1b: Motor summary table.

NR	F-Lat (ms)	L-R F-Lat (ms)
Right Peroneal (EDB)		
	48.00	
Left Tibial (Abd Hallucis)		
NR		
Right Tibial (Abd Hallucis)		
NR		
Right Ulnar (Abd Dig Min)		
	35.26	

Table 1c: F Wave studies.

Side	Muscle	Nerve	Root	Ins Act	Fibs	Psw	Amp	Dur	Poly	Recruit	Int Pat
Right	Ant Tibialis	Deep Peron	L4-5	Nml	1+	1+	Incr	2+	2+	Rapid	Nml
Right	Vastus Med	Femoral	L2-4	Nml	2+	Nml	Decr	1+	1+	Rapid	Nml

Table1d: EMG.

Interpretation: There is electrophysiological evidence of a generalised sensorimotor neuropathic process affecting lower limbs more than upper limbs. There are features suggestive of an underlying demyelinating process, reduced velocity and prolonged F waves. However there is also axonal damage. EMG needle testing shows active denervation with reinnervation which is consistent with an active process.

A 61-year-old man was diagnosed with a recurrent NSCLC squamous-cell type of left upper lobe of lung 4 months ago and had first-line chemotherapy that he completed 1 month ago. His recent positron emission tomography (PET) scan post-chemotherapy had shown progression of his tumour. He was then commenced on Nivolumab of which he had his first dose 1 week ago. He developed dysaesthesia (numbness and tingling) in his lower limbs 3 days ago that rapidly progressed to bilateral lower limb weakness within 48 hours making him unable to walk and wheel chair-bound by the time he presented to emergency department. This is on the background of 60 pack years of smoking and a primary NSCLC in the right upper lobe of the lung 2 years ago for which he had chemoradiotherapy (Carboplatin and Paclitaxel) with good results at the time. His comorbidities included type-2 Diabetes Mellitus and Gout. He denied having any coryzal symptoms or diarrhoea preceding his weakness. Neurological examination, the patient was afebrile and revealed a preserved consciousness along with a power of 2/5 in proximal and distal muscle groups in both upper and limbs. There was a loss of deep tendon reflexes in all 4 limbs along with a peripheral neuropathy in stocking-pattern. Rest of the neurological exam was unremarkable with no meningeal irritation signs. Laboratory findings including inflammatory markers were unremarkable. A magnetic resonance imaging of whole spine revealed spondyloarthropathy at C4/5 and C5/6 regions and old wedge fractures of vertebral bodies at T7 and T8 with no involvement of spinal cord at any level. Nerve conduction studies showed generalised sensorimotor neuropathic process affecting both lower limbs and upper limbs with features suggestive of a demyelinating process (Tables 1a-1d). These pathological findings are consistent with a diagnosis of the acute inflammatory demyelinating polyneuropathy. A cerebrospinal fluid (CSF) analysis was not performed as according to World Health Organisation-Uppsala Monitoring Centre system for standardised case causality assessment, with a plausible time- relationship to Nivolumab injection and absence of other systemic symptoms, it was almost certain that demyelinating symptoms were secondary to Nivolumab [4]. Upon ceasing Nivolumab and initiating treatment with IVMP 1 gram for 5 days, there was a dramatic improvement in his symptoms and he was discharged home after 5 days. Clinical recovery was nearly complete after 5 days and the patient was completely back to normal by the time of his next clinic appointment in 4 weeks. Prednisolone was tapered off gradually over 2 weeks.

Anti PD-1 medications are known to cause immune-related adverse events including an immune-mediated Guillain-Barre-like disorder (GBLD) that instead of intravenous immunoglobulins (IVIGs), is managed with high dose corticosteroids [3]. Predisposing factors for the development of the GBLD in patients treated with Nivolumab are not evident while other immunotherapeutic antibodies with a different

mode of action have been associated with the same. Antibodies directed against cell-surface gangliosides expressed in human peripheral nerve axon sheath have been linked to the pathophysiology of demyelination although mechanism is not clear, however, immune activation by Nivolumab may cause the demyelination by braking peripheral tolerance to such ganglioside-related epitopes in patients with pre-existing humoral autoimmunity against them [5].

Checkpoint inhibitors including PD-1 inhibitors in the treatment of NSCLC and other malignancies are being increasingly used and are entering routine oncological practice, and with the number of patients exposed to these drugs increasing dramatically, IRAEs are becoming more common as well. Clinicians and junior doctors should be aware of these possible rare adverse effects and their management. AIDP is rare but potentially debilitating and possibly life-threatening adverse event and while high-dose IVIGs or plasmapheresis is the recommended therapeutic option for classic Guillain-Barre syndrome (GBS), a treatment with high dose IVMP is the mainstay of the treatment for immune-mediated acute GBLD, which is considered to be non-active in the classical presentation of GBS.

References

1. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, et al. (2016) Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 54: 139-148.
2. Cauchi M, Nikitas N (2015) Diarrhea and generalized weakness in a patient with metastatic melanoma and a lumbosacral mass, after initiation of therapy with a checkpoint inhibitor: A case report. Int J Case Rep Images 6: 682-685.
3. www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf
4. http://who-umc.org/Graphics/24734.pdf
5. Bot I, Blank CU, Boogerd W, Brandsma D (2013) Neurological immune-related adverse events of ipilimumab. Pract Neurol 13: 278-280.