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Review article

Immune mediated neuropathy following checkpoint immunotherapy

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ABSTRACT

Checkpoint immunotherapy has revolutionised cancer therapy and is now standard treatment for many malignancies including metastatic melanoma. Acute inflammatory neuropathies, often labelled as Guillain-Barre syndrome, are an uncommon but potentially severe complication of checkpoint immunotherapy with individual cases described but never characterised as a group. We describe a case of acute sensorimotor and autonomic neuropathy following a single dose of combination ipilimumab and nivolumab for metastatic melanoma. A literature search was performed, identifying 14 other cases of acute neuropathy following checkpoint immunotherapy, with the clinical, electrophysiological and laboratory features summarised. Most cases described an acute sensorimotor neuropathy (92%) with hyporeflexia (92%) that could occur from induction up till many weeks after the final dose of therapy. In contrast to Guillain-Barre syndrome, the cerebrospinal fluid (CSF) analysis often shows a lymphocytic picture (50%) and the electrophysiology showed an axonal pattern (55%). Treatment was variable and often in combination. 11 cases received steroid therapy with only 1 death within this group, whereas of the 4 patients who did not receive steroid therapy there were 3 deaths. In conclusion checkpoint immunotherapy – induced acute neuropathies are distinct from and progress differently to Guillain-Barre syndrome. As with other immunotherapy related adverse events corticosteroid therapy should be initiated in addition to usual therapy.

1. Introduction

Checkpoint immunotherapies are now standard treatment for many cancers including advanced melanoma, lung cancer, kidney cancer, head and neck cancer, and bladder cancer [1]. These therapies remove T-cell inhibitory pathways resulting in upregulation of the anti-tumour immune response, with the potential consequence being immune-related adverse events (irAEs) in normal tissues [2]. Peripheral neuropathy is uncommon but cases of severe "Guillain-Barre syndrome" (GBS) resulting in death have been reported.

2. Methods

We provide a detailed description of a case of acute sensorimotor and autonomic polyneuropathy following administration of a single dose of combination ipilimumab and nivolumab for metastatic melanoma. A MEDLINE search was performed of previous publications in English for text word and MeSH headings of "neuropathy", "Guillain-Barre Syndrome" and "ipilimumab", "nivolumab", "pembrolizumab", "CTLA-4" or "PD-1". The references and citations of retrieved articles were all reviewed with relevant cases included for analysis of reported clinical, investigational and treatment findings.

3. Case vignette

A 49-year-old woman with NRAS-mutant metastatic melanoma to chest wall, lung, and retroperitoneal and axillary nodes was commenced on combination ipilimumab (3 mg/kg) and nivolumab (1 mg/kg). Five days following induction she developed painful

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paresthesiae in the extremities, progressing over four days to a symmetrical sensorimotor and autonomic neuropathy with proximal loss of antigravity power and loss of independent mobility (Fig. 1. Clinical course). Reflexes were absent and sensory loss was present to the upper arms and knees bilaterally. Two days after her developing sensory symptoms, she experienced a fever and a brief episode of diarrhea. Blood and stool cultures were negative and symptoms resolved promptly.

Initial electrodiagnostics suggested an acute generalized motor predominant neuropathy with patchy slowing of conduction velocity (Table 1). MRI of the whole spine was normal. Cerebrospinal fluid (CSF) analysis showed increased protein (1.15 g/L), 15 white blood cells (93% lymphocytes), one erythrocyte, no oligoclonal bands, negative cryptococcal antigens, normal culture and cytology. Serum anti-GM1 ganglioside antibodies were negative. Routine full blood count, biochemistry, glucose, B12, folate, renal, liver and thyroid function tests were normal. Serology for HIV and syphilis were negative. Serum immunofixation showed no monoclonal protein. The ANA and ANCA were negative, and levels of CRP, ESR, C3 and C4 were normal.

She commenced IV immunoglobulin (IVIG, 0.4 g/kg/d for 5 days) and IV methylprednisolone (1 g/d for 5 days, then 500 mg/d for 3 days) followed by tapering oral prednisone (1 mg/kg/d). Symptoms stabilized with mild improvement yet one month later she developed worsening weakness and ongoing painful paresthesia. She also developed persistent nausea coupled with postural hypotension and constipation. After the exclusion of structural and metabolic causes, this was thought to represent an autonomic neuropathy.

Another course of IVIG and IV methylprednisone were given with slight but non-sustained improvement. Repeat electrodiagnostics demonstrated an axonal predominant sensorimotor neuropathy. A third course of IV methylprednisone and plasma exchange (PLEX, five exchanges over two weeks, followed by weekly exchanges) was commenced, oral corticosteroids were continued and mycophenolate (1 g bd) was added. Immediate improvements were noted in sensory and autonomic symptoms, followed by a gradual improvement in motor strength. By 6 weeks after commencing PLEX (12 weeks after initial treatment) the patient had only mild weakness and could perform her usual daily activities, and at four months she returned to work with her melanoma in deep partial response: complete response in several lesions, and with only a chest wall and lung metastasis remaining (both smaller than at baseline and with a cystic central component). Prednisone was weaned to 10mg daily and mycophenolate was continued at 1 g BD.

PLEX was ceased at five months after initial checkpoint immunotherapy after her Vascath was complicated by a Pseudomonas aeruginosa infection necessitating removal. At seven months her cystic chest wall and lung lesions slightly increased in size, with aspiration and partial resection of the chest wall lesion finding pigment laden macrophages only. Mycophenolate was weaned to 500 mg daily and prednisone maintained at 10 mg daily.

Table 1
Nerve conduction studies.

	Day 4	Day 39	Day 226
Median nerve – Right			
Motor Latency, APB-Wrist	**5.2**	**5.1**	4.3
CMAP amplitude, wrist	6.8	**2.9**	6.3
CMAP amplitude, elbow	6.0	**2.4**	6.3
Motor CV	42	**33**	48
SNAP amplitude	14	**2**	**4**
Ulnar nerve – Right			
Motor Latency, ADM–Wrist	3.5	3.4	3.1
CMAP amplitude, wrist	10.4	5.1	11.1
CMAP amplitude, above elbow	9.5	4.2	10.3
Motor CV	50	52	53
SNAP amplitude	20	**NR**	**3**
Peroneal nerve – Right			
Motor Latency, EDB-Ankle	5.6	4.4	
CMAP amplitude, ankle	3.8	**0.3**	
CMAP amplitude, fibular head	2.8	**0.3**	
Motor CV	37	40	
Tibial nerve – Right			
Motor Latency, AH-Ankle	5.1	**8.0**	
CMAP amplitude, ankle	**2.1**	**0.4**	
CMAP amplitude, knee	**1.3**	**0.3**	
Motor CV	41	46	
Sural nerve			
Right SNAP amplitude	11	**5.0**	
Left SNAP amplitude	13	**2.0**	**4.0**

CMAP: Compound muscle action potential, **CV:** Conduction velocity, **SNAP:** Sensory nerve action potential.

At nine months the two remaining melanoma metastases (lung and chest wall) started to enlarge with a cystic central component. Due to this fact, the extended time interval from initial toxicity, and because she was minimally symptomatic with electrodiagnostics showing partial recovery, her remaining mycophenolate was ceased. Within one week of cessation sensory neurological symptoms flared and corticosteroid and mycophenolate was recommenced. This improved symptoms and sequential imaging demonstrated further regression of melanoma.

After a few months of clinical stability (prednisone 25 mg daily, mycophenolate 500 mg bd), tapering of her steroid dose was recommenced which soon resulted in increasing pain, weakness and glove and stocking numbness to her elbows and knees. With a further poor response to IVIG and 50 mg per day of prednisone, she was commenced on rituximab infusion (375 mg/m^2 weekly for four weeks). There was no clinical response after rituximab infusion and she has since recommenced plasma exchange with an increased dose of mycophenolate (1.5 g bd) and prednisone.

In summary we describe a case of acute peripheral neuropathy occurring after the administration of combination checkpoint immunotherapy for metastatic melanoma. The case provides a

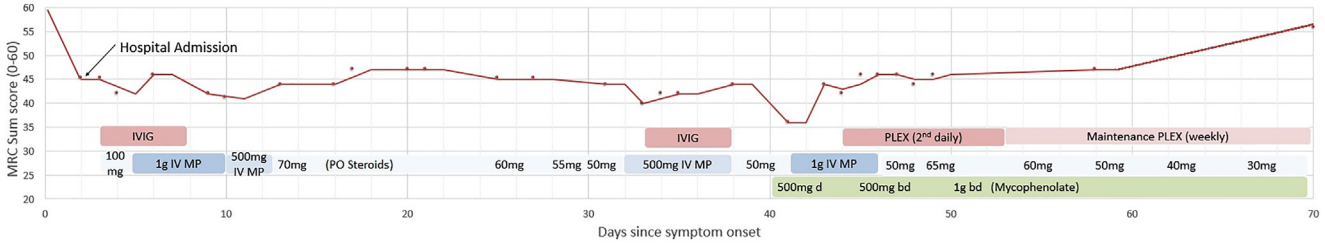

Fig. 1. A graphical representation of the patient's motor polyneuropathy and the clinical response to acute therapies. MRC sum score: Medical Research Council sum score comprised of the sum of the MRC grades of deltoid, biceps, wrist extensor, iliopsoas, quadriceps femoris and tibialis anterior bilaterally (0–60). IVIG: Intravenous Immunoglobulin. PLEX: Plasma exchange. IV MP: Intravenous Methylprednisone. PO: per os; oral administration.

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