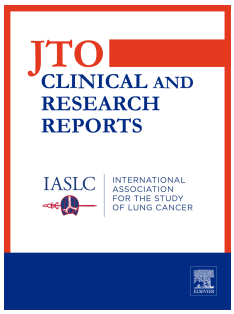

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PD-1 Inhibitor-Mediated Peripheral Neuropathy

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Abstract: The discovery of immune checkpoint inhibitors (ICIs) has revolutionized the model of antitumor therapy. With the continuous deepening of the research on the mechanism of immunotherapy, immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors and CTLA4/CD28 inhibitors, have been widely used in a variety of tumors. However, the use of ICI can also lead to a series of immune-related adverse events (irAEs). Common immune-related adverse events include gastrointestinal toxicity, pulmonary toxicity, endocrine system toxicity, skin toxicity and so on. Neurological adverse events are relatively rare, but they seriously affect the quality of life and shorten the survival time of patients. This paper reports cases of peripheral neuropathy mediated by PD-1 inhibitors, and retrieves the relevant literatures at home and abroad to summarize the neurotoxicity caused by PD-1 inhibitors, so as to strengthen the awareness of clinicians and patients on neurological adverse reactions and mitigate potential adverse effects of implemented therapies.

Key words: PD-1; Immunotherapy; Neurotoxicity; Peripheral neuropathy

With the advent of the immune era, ICI monotherapy or combined chemotherapy has gradually been widely used in a variety of malignant tumors. ICIs currently available on the market include cytotoxic T lymphocyte associated protein 4 (CTLA-4) inhibitors, programmed cell death protein 1 (PD-1) inhibitors and programmed cell death-ligand 1 (PD-L1) inhibitor. PD-1 is the most common immune checkpoint inhibitor, and is widely used in non-small cell lung cancer, esophageal cancer, stomach cancer, liver cancer, melanoma and other tumors. However, the application of PD-1 inhibitors can improve the therapeutic efficacy of cancer patients, but at the same time, a series of adverse reactions may occur. In this paper, two cases of peripheral neuropathy mediated by PD-1 inhibitors were analyzed and reported, in order to provide a reference for the early recognition and management of neurotoxicity.

Method:

Patients with PD-1 treatment and neurological adverse reactions in our hospital were collected, and two patients with peripheral neuropathy were reported in detail. All data were obtained with the informed consent of patients. Then we reviewed and summarized literatures related to immunotherapy-induced neurotoxicity.

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Case 1

The 57-year-old male patient was admitted to the hospital on March 14, 2022 due to "adenocarcinoma of the right lung for more than one year and weakness of both lower limbs for more than one month". The patient was found to have right pulmonary nodules during chest CT scan in 2014, and was not treated after intermittent reviews. Cough and expectoration occurred in October 2020. Chest CT showed multiple masses and nodules in the lung, some of which were enlarged compared with the previous ones. Mediastinal lymph nodes were slightly enlarged. Biopsy of the right lung was performed and pathology showed invasive adenocarcinoma (right lung) with local features of mucinous adenocarcinoma. Gene detection showed EGFR/ALK/ROS1/c-MET wild type, BRAF, TP53 mutation, TMB 21.3 Muts/Mb, MSS. Family history and personal history are not special.

From December 24, 2020, 6 cycles of pemetrexed and cisplatin (PP) plus PD-1 regimen were given, specifically: pemetrexed 900mg iv D1 + cisplatin for injection 130mg iv D1 + Toripalimab monoclonal antibody (Junshi Biological) 240mg iv D2. After 2, 4 and 6 cycles, the efficacy was evaluated as PR (Figure 1a-b). On May 24, 2021, the patient received maintenance therapy of pemetrexed 900mg iv D1 plus of Toripalimab monoclonal antibody 240mg iv D2 for one cycle, and then the patient requested to replace Toripalimab with Sintilimab due to economic reasons. On June 18, 2021, the patient was treated with the 8th cycle of pemetrexed 900mg iv D1 plus of Sintilimab 200mg iv D2. Then comprehensive review showed some of the lung metastases were enlarged compared with the previous ones, and PD was evaluated for efficacy.

From July 12, 2021, it was adjusted to the second-line therapy: pemetrexed 900mg iv D1 plus Sintilimab 200mg iv D2 and Anlotinib 12mg PO 2 weeks, rest for 1 week, regular treatment for 9 times, the last treatment time was February 6, 2022, during which the lesion remained stable. After the last treatment, the patient complained of numbness and weakness in the limbs, especially in the lower limbs, and difficulty in standing up after squatting. He was admitted to hospital for further diagnosis and treatment.

Physical examination on admission: T 36.5℃, HR 78 beats/min, R 17 beats/min, BP 128/84mmHg, conscious and in good spirits. Nervous system examination: cranial nerve examination showed no obvious abnormality, bilateral pupils were 2.5mm in diameter, and they were sensitive to light. Muscle strength of both upper limbs was grade 5-, proximal end of both lower limbs was grade 4, and distal end was grade 5-. There was a symmetrical presence of deep and superficial sensations, and tendon reflexes in the limbs were reduced. Hofferman's sign (-) for both upper limbs and Babinski's sign (-) for both lower limbs.

Blood routine and biochemical tests after admission showed no obvious abnormality. Electromyography (both lower limbs): 1. Neurogenic damage of both lower limbs. (Spontaneous potential can be seen in the left lower limb) 2. The amplitude of the right accessory nerve decreases with low frequency stimulation. (Among them, 7Hz decreases by 9.9%, and 10Hz decreases by 12.8%). (Both upper limbs) Neurogenic damage to the left biceps brachii and bilateral first interosseous muscles (Table 1). No clear signs of metastases were seen in the brain MRI. We considered the possibility of PD-1 related neurotoxicity, lumbar puncture was performed. The cerebrospinal fluid was clear and transparent, the cell count was 0, and the cerebrospinal fluid protein was negative. Biochemical examination showed that the cerebrospinal fluid protein, chloride and glucose was in normal limits. The cerebrospinal fluid was sent to the Neuroimmune Laboratory of Peking University First Hospital for relevant examination. The results showed that

the oligoclonal band (OCB) of cerebrospinal fluid and blood was positive (the same as the blood band, type IV), and the IgG index, AQP4 antibody, ganglioside ester spectrum antibody, AchR antibody and MAG antibody were all negative (Supplementary Table).

Table 1 EMG result of case 1

A. Motor Nerve Conduction Studies

Nerve	Lat (ms)	Amp (mV)	CV (m/s)	Dist (mm)	Lat Diff (m/s)
Tibial nerve left					
Ankle-AH	3.29	31.2			
Popliteal fossa-ankle	10.9	19.7	51.2	390	7.6
Tibial nerve right					
Ankle -AH	3.02	26.0			
Popliteal fossa-ankle	11.4	21.0	46.5	390	8.4
common peroneal nerve left					
Ankle -EDB	3.42	7.1			
fibular head inferior-ankle	10.3	7.5	47.2	325	6.9
Tibialis anterior muscle recording	3.45	8.0			
common peroneal nerve right					
Ankle-EDB	3.58	4.0			
fibular head inferior-ankle	10.3	3.7	48.4	325	6.7
Tibialis anterior muscle recording	3.57	9.7			
ulnar nerve left					
Wrist -ADM	2.75	15.6			
elbow-wrist	7.98	15.5	55.4	290	5.2
ulnar nerve right					
Wrist -ADM	2.71	14.6			
below elbow - wrist	6.40	14.9	50.1	185	3.7
Above elbow - below elbow	8.25	15.0	56.8	105	1.85
Erb- Above elbow	13.3	13.4			
Median nerve left					
Wrist -APB	3.77	10.9			
Elbow-wrist	7.71	10.5	53.3	210	3.9
Median nerve right					
Wrist -APB	3.88	11.4			
Elbow-wrist	7.56	11.0	55.7	205	3.7
axillary-elbow	9.23	10.3	59.9	100	1.67

B. Sensory Nerve Conduction Studies

Nerve	Peak Lat (ms)	Amp (uV)	CV (m/s)	Dist (mm)
Sural nerve left				
Middle calf - lateral malleolus	3.30	8.3	45.5	150
Sural nerve right				
Middle calf - lateral malleolus	3.30	9.1	45.5	150
Ulnar nerve left				
Digital nerve- Wrist	2.48	25.6	50.4	125
Ulnar nerve right				
Digital nerve- Wrist	2.59	31.0	48.3	125
Median nerve left				
Digital nerve II - Wrist	2.67	20.4	54.3	145
Median nerve right				
Digital nerve II - Wrist	2.67	20.2	54.3	145

C. F-Wave

Nerve	F-M Lat	F-Lat	M-Lat	#F	
	ms	ms	ms	#	F%
Left tibial nerve Ankle-AH	44.0	46.3	3.4	20.0	100
Right tibial nerve Ankle-AH	43.6	46.6	3.8	20.0	100
Left ulnar nerve Wrist-ADM	25.5	27.7	3.0	19.0	95.0
Right ulnar nerve Wrist-ADM	24.3	26.9	3.2	19.0	95.0
Left median nerve Wrist-APB	23.2	27.0	4.4	19.0	95.0
Right median nerve Wrist-APB	22.3	26.4	4.5	19.0	95.0

D . EMG MUP Data

	spontaneous potential				amplitude	time limit	Raise phase
	fibrillation	positive phase	fasciculation	CRD	uV	ms	
Left quadriceps	+	++	-	-	1769	16.7	monomiscible
Right quadriceps	-	-	-	-	2475	16.6	monomiscible
Left tibialis anterior	+	++	-	-	1926	16.3	monomiscible
Right tibialis	-	-	-	-	1042	14.1	monomiscible

anterior							
Right gastrocnemius	-	-	-	-	1100	10.9	monomiscible
Left biceps	-	-	-	-	1047	14.7	monomiscible
Left dorsal interosseous muscle I	-	-	-	-	1619	14.5	monomiscible
Right dorsal interosseous muscle I	-	-	-	-	1966	13.9	monomiscible

Treatment: According to the 2021 NCCN/CSCO guidelines, hormones (1-2mg/kg/day, the dosage is adjusted according to the specific situation), gamma globulin impact, plasma exchange, and other immunosuppressants after the hormone is ineffective. The patient could not be hospitalized for treatment due to local coronavirus epidemic situation. He was told to orally take methylprednisolone tablets 80 mg qd at home, and the dose was reduced to 40 mg 3 days later. The patient complained that the symptoms were improved after oral administration of 80 mg hormone for 3 days, and reappeared after dose reduction. After consultation with neurologists, combined with the current examination and test results, myasthenia gravis was not excluded. The patient was advised to take pyridostigmine bromide tablets orally, 60mg bid. Nine days later, the patient was told by telephone that the symptoms of lower limb fatigue were better than before, squatting up, and the lower limb muscle strength was better than before when going upstairs and downstairs. After 40 days of oral administration, the patient's subjective symptoms were improved, and myasthenia did not worsen after withdrawal of pyridostigmine bromide.

Case 2

The 65-year-old female patient was admitted to the hospital on February 20, 2021 due to " small cell lung cancer for 3 months and weakness of the limbs for 15 days". In September 2020, the patient developed cough accompanied by discomfort in the right back, and chest CT showed lung cancer around the right lower lobe with left hilar and mediastinal lymph node metastasis. On December 2, 2020, a biopsy of the right cervical lymph node was performed, and the pathology showed small cell neuroendocrine carcinoma with infiltration and necrosis was seen in the fibrous tissue. Further PET-CT showed that left lower lung cancer and accompanied by multiple lymph node metastases in the right neck, right clavicle, mediastinum, and bilateral hilum.

From December 7, 2020, EC+PD-1 treatment was given for 2 cycles, specifically: etoposide 200mg, 200mg, 100mg iv D1-3 + carboplatin 500mg iv D1 + sintilimab 200mg iv D4. Before the third cycle after chemotherapy, she developed numbness and weakness of the limbs, and was admitted to the hospital for further diagnosis and treatment.

Physical examination on admission: T 36.3°C, HR 74 beats/min, R 18 beats/min, BP 135/81mmHg, conscious and in good spirits. Nervous system examination: cranial nerve examination showed no obvious abnormality, bilateral pupils were 2.5mm in diameter, and they were sensitive to light. Muscle strength of both upper extremities was grade 2, and muscle strength of both lower extremities was 2- grade. The deep and superficial sensations were

symmetrical, and the tendon reflexes of the limbs were reduced. Hofferman's sign (-) for both upper extremities and Babinski's sign (-) for both lower extremities.

Blood biochemical tests after admission: alanine aminotransferase, aspartate aminotransferase, and creatine kinase were within normal limits. EMG shows neurogenic damage of upper and lower extremities. (1. The sensory nerve fibers are mainly involved; 2. Consider cervical and lumbosacral nerve root involvement) (Table 2) Cervical and thoracic MRI showed degenerative changes in the cervical and thoracic spine, and cervical disc herniation. Brain MRI showed no obvious abnormality. Re-examination of chest CT showed that the lesion was smaller than before, and the efficacy was evaluated as Partial Response by RECIST 1.1.

Table 2 EMG results of case 2

A. Motor Nerve Conduction Studies

Nerve	Lat (ms)	Amp (mV)	CV (m/s)	Dist (mm)	Lat Diff (m/s)
Tibial nerve left					
Ankle-AH	4.03	6.9			
Popliteal fossa-ankle	12.1	5.0	45.2	365	8.1
gastrocnemius recording	4.13	17.4			
Tibial nerve right					
Ankle-AH	3.72	7.0			
Popliteal fossa-ankle	12.1	5.0	45.2	365	8.6
gastrocnemius recording	4.06	10.4			
common peroneal nerve left					
Ankle -EDB	3.79	5.6			
fibular head inferior-ankle	11.3	4.4	41.3	310	7.5
fibular capitulum	13.7	4.2	41.7	100	2.4
supra-fibular capitulum					
common peroneal nerve left					
Ankle -EDB	3.54	7.3			
fibular head inferior-ankle	10.8	5.2	42.0	305	7.3
fibular capitulum	13.1	4.8	43.5	100	2.3
supra-fibular capitulum					
Ulnar nerve left					
Wrist -ADM	2.96	14.3			
Below elbow – wrist	6.42	12.9	50.6	175	3.5
Above elbow-below elbow	8.59	12.0	50.7	110	2.2
Axillary - above elbow	10.3	11.7	58.5	100	1.71
Ulnar nerve left					
Wrist -ADM	2.77	14.7			
Below elbow – wrist	6.11	15.1	52.4	175	3.3
Above elbow-below elbow	7.94	15.5	57.4	105	1.83
Axillary - above elbow	9.69	14.4	57.1	100	1.75
Median nerve left					

Wrist-APB	3.73	10.0			
Elbow-wrist	7.58	8.8	55.8	215	3.9
Axillary-elbow	9.88	10.4	56.5	130	2.3
Erb- axillary	14.0	10.6	61.9	255	4.1
Median nerve right					
Wrist-APB	3.96	9.2			
Elbow-wrist	7.90	7.8	54.6	215	3.9
Axillary-elbow	10.1	9.4	59.1	130	2.2
Erb- axillary	14.3	8.7	60.7	255	4.2

B. Sensory Nerve Conduction Studies

Nerve	Peak Lat (ms)	Amp (uV)	CV (m/s)	Dist (mm)
Sural nerve left				
Middle calf - lateral malleolus	4.22	1.14	34.4	145
Sural nerve right				
Middle calf - lateral malleolus	3.86	0.44	38.9	150
Ulnar nerve left				
Digital nerve- Wrist	2.95	1.83	40.7	120
Ulnar nerve right				
Digital nerve- Wrist	2.98	1.40	40.3	120
Median nerve left				
Digital nerve II - Wrist	3.06	5.3	49.0	150
Median nerve right				
Digital nerve II - Wrist	3.09	2.9	48.5	150

C. F-Wave

Nerve	F-M Lat	F-Lat	M-Lat	#F	
	ms	ms	ms	#	F%
Left tibial nerve Ankle-AH	52.1	56.7	5.3	20.0	100
Right tibial nerve Ankle-AH	50.8	55.3	5.4	20.0	100
Left ulnar nerve Wrist-ADM	26.6	28.6	2.8	20.0	100
Right ulnar nerve Wrist-ADM	26.1	28.5	3.0	20.0	100
Left median nerve Wrist-APB	24.6	27.4	3.7	20.0	100

Right median nerve Wrist-APB	24.8	27.8	3.8	20.0	100

D．EMG MUP Data

	spontaneous potential				amplitude	time limit	Raise phase
	fibrillation	positive phase	fasciculation	CRD	uV	ms	
Left quadriceps	+	++	-	-	1769	16.7	monomiscible
Right quadriceps	-	-	-	-	2475	16.6	monomiscible
Left tibialis anterior	+	++	-	-	1926	16.3	monomiscible
Right tibialis anterior	-	-	-	-	1042	14.1	monomiscible
Right gastrocnemius	-	-	-	-	1100	10.9	monomiscible
Left biceps	-	-	-	-	1047	14.7	monomiscible
Left dorsal interosseous muscle I	-	-	-	-	1619	14.5	monomiscible
Right dorsal interosseous muscle I	-	-	-	-	1966	13.9	monomiscible

Treatment: The numbness and weakness of the patient's limbs were considered as immune-mediated peripheral neuropathy. According to the recommendations of CSCO guidelines, methylprednisolone, tocilizumab and human immunoglobulin therapy were given after admission, and the symptoms improved slightly. Nervous system examination after treatment: muscle strength of both upper extremities was grade 3, and muscle strength of both lower extremities was 3- grade. The other physical examinations were the same as admission.

Discussion

With the advent of the immune era, people’s understanding of immune checkpoint inhibitors (ICIs) has gradually deepened, and the application of ICI has gradually become widespread. However, immune checkpoint inhibitors are a double-edged sword. ICI not only acts on the tumor microenvironment, but also affects systemic immune cells. Circulating activated T cells targeting autoantigens and/or inflammatory cytokines may lead to inflammation and/or destruction of peripheral tissues, leading to clinical symptom of autoimmune diseases. Most patients treated with checkpoint inhibitors develop some form of immune-related toxicity. Almost all organ systems have been affected, with the most common irAE involving the skin or gastrointestinal system[2].

Immunotherapy-associated neurotoxicity is a rare adverse reaction, occurring in 3.8% of patients treated with CTLA-4, 6.1% of patients treated with PD-1 inhibitors, and 12% in combination therapy[3]. The specific mechanism of adverse reactions of nervous system caused by immune checkpoint inhibitors is still unclear, but Fellner et al. proposed two theories, the first

possible explanation is that some patients suffer from subclinical autoimmune diseases before immunotherapy, but because the body's immune tolerance does not have obvious clinical symptoms, this immune balance will be broken after the application of ICI. Increased autoimmune reactions produce the corresponding symptoms. Another possible explanation is that there are cross reactions between nervous system antigens and tumor-associated antigens, and activated T cells after ICI attack tumor cells will affect the nervous system[4].

The adverse reactions of the nervous system are various and have different clinical manifestations. Central nervous system, peripheral nervous system diseases and neuromuscular junctions can occur adverse reactions of the nervous system, ranging from various non-specific symptoms such as fatigue, headache, dizziness, paresthesia to various clinical syndromes such as myasthenia gravis, Guillain-Barre syndrome, aseptic meningitis, encephalitis, transverse myelitis and so on[2]. The diagnostic process of immune-related neurotoxicity is complex and needs to be determined by combining the patient's medical history, neurological examination, brain MRI, Electromyography, and cerebrospinal fluid examination, and neurological diseases caused by other causes, such as paraneoplastic syndrome, neurological metastasis, infection diabetes, are excluded.

The onset time of neurological adverse reactions varies from several days to several months, with an average onset time of 45 days[5] . Most of them are non-specific symptoms of grade 1 to 2. The incidence of severe neurotoxicity (grade 3 to 5) is only less than 1%[6]. However, neurological symptoms affect the quality of life and may lead to long-term or permanent sequelae. Severe neurotoxicity can progress rapidly to death. The myasthenia gravis (MG) has earlier average onset time, and can occur within 2 weeks after ICI treatment, as well as is often accompanied by myocarditis and myositis[7]. Severe symptoms can endanger the medulla oblongata and respiratory muscles, resulting in swallowing and respiratory dysfunction, and higher fatality rate[8].

PD-1 inhibitor-associated neurotoxicities reported in the previous literature were reviewed and searched in CNKI, Wanfang Data, Pubmed and other databases by using "neurotoxicity", "immune checkpoint inhibitors (ICIs)", "neurological adverse reactions", "PD-1", 'ICI', "neurotoxicity", "neurological complication", and "neurological adverse events" as keywords. Due to the low incidence of neurotoxicity, it has not been fully reported in a number of large phase III clinical trials in China. Therefore, most of the search results were pembrolizumab and nivolizumab-related adverse reactions, and less neurotoxicity was reported with domestic PD-1 drugs such as Toripalimab, Sintilimab and tislelizumab. We collected relevant literature and counted the number of cases of neurological adverse reactions in each literature (Table 3). Among the reported adverse reactions of nervous system, peripheral neuropathy (21.4%), encephalitis (28.9%) and neuromuscular junction diseases (38.6%) have relatively high incidence. A retrospective analysis of neurotoxicities with nivolizumab showed 53.7% of which were peripheral neuropathy, 12.2% were encephalitis, 12.2% were meningitis, 7.3% were myasthenia gravis, and 14.6% were nonspecific symptoms[9]. PD-1 has a higher incidence of developing immune-related encephalitis versus CTLA-4 inhibitors, whereas meningitis is predominantly seen in patients taking CTLA-4 inhibitors[10].

Table 3 PD-1 associated nervous system adverse reactions (number of cases)

References	PD-1	Peripheral neuropat	CNS			Neuromuscular junction	Nonspecific sympto
			Demyelination	Encephalitis/myel	meningitis		

		hy	disease	itis		disease	m
Feng et al.,2017[11]	Pembro	2		3			
	Nivo		1	2		1	
Larkin et al.,2017[9]	Nivo	22		5	5	3	6
Kao et al.,2017[12]	Pembro	3		1			
	Nivo	1					1
Vitt et al.,2018[13]	Pembro			1			
Sato et al.2019[14]	Pembro	34		20	10	32	
	Nivo	53		26	6	55	
Johnson et al.,2019[5]		64		186	36	197	
Vogrig et al.,2020[15]	Pembro			4	1		1
	Nivo			5	2		1
Kolb et al.,2018[16]	Pembro/ Nivo					2	
Fellner et al.,2018[4]	Pembro	1					
	Nivo	1		3		1	
Zhao et al.,2021[17]	Pembro	4		6			
	Nivo	6		22	2	51	
	Cemi			1			
Xu xiaoting et, 2021[18]	Pembro					1	
Wang weilan et, 2021[19]	toripalimab					1	

Peripheral neuropathy refers to structural and functional impairments of peripheral motor, sensory, and autonomic nerves. Patients may present with pain, paresthesia, and decreased muscle strength. Guillain-Barre syndrome (GBS) is more common in nervous system caused by ICI. Cell-protein segregation in cerebrospinal fluid is a characteristic finding of GBS. Peripheral nerves are composed of neurons and nerve fibers emanating from them and can be divided into motor neurons, sensory neurons, autonomic ganglia, nerve roots, and plexus lesions according to anatomical sites. The etiology of peripheral neuropathy is complex, including hereditary, toxic metabolic, infectious disease, endocrine disease, immune-mediated, tumor, malnutrition, iatrogenic and idiopathic[20]. ICI-induced peripheral neuropathy is immune-mediated, which is associated with a variety of autoantibodies, such as ganglioside antibodies, anti-fascin antibodies, anti-contactin antibodies, and anti-contactin associated protein-2 antibodies[21].

In case 1, patient developed new symptoms of limb weakness after more than one year of antineoplastic therapy, and had no previous history of diabetes mellitus, autoimmune diseases, etc. The antineoplastic therapy was effective as a whole, and the cerebrospinal fluid paraneoplastic antibodies were negative, so paraneoplastic syndrome could be excluded; the patient had no signs of metastasis on brain MRI, which could exclude symptoms caused by tumor progression and brain metastasis. Myositis could be excluded as the patient's Electromyography showed

neurogenic damage, no myogenic damage, and CK was within the normal range; the patient had sudden symptoms of limb weakness after one year of anti-tumor treatment, and the type and dose of chemotherapy drugs did not reach the limiting neurotoxic dose, so peripheral nerve injury caused by chemotherapy drugs was not considered temporarily. The patient showed muscle weakness, and the Electromyography showed that the amplitude of the right accessory nerve presented a decreasing trend when it was stimulated at low frequency. (Among them, 7Hz decreases by 9.9%, and 10Hz decreases by 12.8%). Laboratory tests showed that AchR antibody was negative, and there was no typical manifestation of myasthenia gravis, such as light in the morning and heavy in the evening. Myasthenia gravis was improved after oral administration of pyridostigmine bromide tablets, but was not aggravated after withdrawing pyridostigmine bromide tablets. Therefore, the diagnosis of myasthenia gravis can be ruled out. The Electromyography of the patient suggested that the neurogenic damage, the muscle strength of the limbs was decreased, and the tendon reflex was reduced, which could be located as the injury of lower motor neurons and peripheral nerves. Further examination of cerebrospinal fluid showed that oligoclonal bands (OCB) in cerebrospinal fluid and blood were positive (Type IV)(Table 4), suggesting that there might be activation of the systemic immune system or increased permeability of the blood-brain barrier[22],but the patient had no obvious myelitis manifestations and cerebrospinal fluid cell-protein isolation in GBS, which might be related to radiculopathy. So according to the clinical signs and auxiliary examination results, peripheral neuropathy caused by immune-mediated nerve root injury was the first consideration.

In case 2, patient developed numbness and weakness in the limbs after 2 cycles of anti-tumor treatment. The onset of the patient was rapid and the symptoms were severe. Chest CT showed that antitumor therapy was effective and combined with other auxiliary examinations, it was possible to exclude tumor progression, paraneoplastic syndrome, myositis, and neurological diseases caused by other reasons. As a consequence, drug-related neurotoxicity is still considered. Since the doses of etoposide and carboplatin did not reach the limiting neurotoxic dose, combined with EMG results (neurogenic damage of upper and lower extremities), it was considered as immune-mediated peripheral neuropathy.

Peripheral neuropathy of ICI therapy is a very notable adverse reaction. It is important to make a clear diagnosis through history, imaging and cerebrospinal fluid examination. For mild cases, stop immunotherapy and taking hormone therapy may provide good results. As for severe cases, the prognosis is usually poor, hormones, gamma globulin impact, plasma exchange, and other immunosuppressants are necessary.

Table 4 Oligoclonal band (OCB) typing and clinical significance

Typing	Result	Clinical significance
Type I	OCB was not detected in cerebrospinal fluid and serum	No associated immune disorders had been present.
Type II	OCB was present in cerebrospinal fluid but not in serum	It is commonly seen in multiple sclerosis, autoimmune encephalitis, optic neuromyelitis, and some special infections.
Type III	OCB was present in cerebrospinal fluid and serum, but there was an additional zone in CSF	It is seen in encephalomyelitis, ADEM,

		acute myelitis and viral encephalitis infected by special pathogens.
Type IV	Identical OCBs in cerebrospinal fluid and serum	It can be seen in patients with inflammatory demyelinating disease of the spinal cord, GBS, and leukemia after transplantation.
Type V	Identical monoclonal bands in cerebrospinal fluid and serum	It usually occurs in some patients with hematological diseases, poems, monoclonal gammaglobulinemia (MGUS) -related peripheral neuropathy

Summary

Although neurotoxicity associated with immune checkpoint inhibitors is rare, the impact on patients' quality of life cannot be ignored and may be life-threatening if not diagnosed and treated properly. At present, there are few reports on PD-1-related neurotoxicity made in China. In this paper, cases of peripheral neuropathy caused by Toripalimab with Sintilimab was analyzed, and the literatures on PD-1-mediated neurotoxicity were collected and summarized, hoping that the PD-1-mediated neurotoxicity can be identified, diagnosed and treated in clinical practice to ensure the safety of patients during the anti-tumor treatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table 1 EMG result of case 1

A. Motor Nerve Conduction Studies

Nerve	Lat (ms)	Amp (mV)	CV (m/s)	Dist (mm)	Lat Diff (m/s)
Tibial nerve left					
Ankle-AH	3.29	31.2			
Popliteal fossa-ankle	10.9	19.7	51.2	390	7.6
Tibial nerve right					
Ankle -AH	3.02	26.0			
Popliteal fossa-ankle	11.4	21.0	46.5	390	8.4
common peroneal nerve left					
Ankle -EDB	3.42	7.1			
fibular head inferior-ankle	10.3	7.5	47.2	325	6.9
Tibialis anterior muscle recording	3.45	8.0			
common peroneal nerve right					
Ankle-EDB	3.58	4.0			
fibular head inferior-ankle	10.3	3.7	48.4	325	6.7
Tibialis anterior muscle recording	3.57	9.7			
ulnar nerve left					
Wrist -ADM	2.75	15.6			
elbow-wrist	7.98	15.5	55.4	290	5.2
ulnar nerve right					
Wrist -ADM	2.71	14.6			
below elbow - wrist	6.40	14.9	50.1	185	3.7
Above elbow - below elbow	8.25	15.0	56.8	105	1.85
Erb- Above elbow	13.3	13.4			
Median nerve left					
Wrist -APB	3.77	10.9			
Elbow-wrist	7.71	10.5	53.3	210	3.9
Median nerve right					
Wrist -APB	3.88	11.4			
Elbow-wrist	7.56	11.0	55.7	205	3.7
axillary-elbow	9.23	10.3	59.9	100	1.67

B. Sensory Nerve Conduction Studies

Nerve	Peak Lat (ms)	Amp (uV)	CV (m/s)	Dist (mm)

Sural nerve left				
Middle calf - lateral malleolus	3.30	8.3	45.5	150
Sural nerve right				
Middle calf - lateral malleolus	3.30	9.1	45.5	150
Ulnar nerve left				
Digital nerve- Wrist	2.48	25.6	50.4	125
Ulnar nerve right				
Digital nerve- Wrist	2.59	31.0	48.3	125
Median nerve left				
Digital nerve II - Wrist	2.67	20.4	54.3	145
Median nerve right				
Digital nerve II - Wrist	2.67	20.2	54.3	145

C. F-Wave

Nerve	**F-M Lat**	**F-Lat**	**M-Lat**	**#F**	
	ms	ms	ms	#	F%
Left tibial nerve Ankle-AH	44.0	46.3	3.4	20.0	100
Right tibial nerve Ankle-AH	43.6	46.6	3.8	20.0	100
Left ulnar nerve Wrist-ADM	25.5	27.7	3.0	19.0	95.0
Right ulnar nerve Wrist-ADM	24.3	26.9	3.2	19.0	95.0
Left median nerve Wrist-APB	23.2	27.0	4.4	19.0	95.0
Right median nerve Wrist-APB	22.3	26.4	4.5	19.0	95.0

D . EMG MUP Data

	spontaneous potential				**amplitude**	**time limit**	**Raise phase**
	fibrillation	positive phase	fasciculation	CRD	uV	ms	
Left quadriceps	+	++	-	-	1769	16.7	monomiscible
Right quadriceps	-	-	-	-	2475	16.6	monomiscible
Left tibialis anterior	+	++	-	-	1926	16.3	monomiscible
Right tibialis anterior	-	-	-	-	1042	14.1	monomiscible

Right gastrocnemius	-	-	-	-	1100	10.9	monomiscible
Left biceps	-	-	-	-	1047	14.7	monomiscible
Left dorsal interosseous muscle I	-	-	-	-	1619	14.5	monomiscible
Right dorsal interosseous muscle I	-	-	-	-	1966	13.9	monomiscible

Table 2 EMG results of case 2

A. Motor Nerve Conduction Studies

Nerve	Lat (ms)	Amp (mV)	CV (m/s)	Dist (mm)	Lat Diff (m/s)
Tibial nerve left					
Ankle-AH	4.03	6.9			
Popliteal fossa-ankle	12.1	5.0	45.2	365	8.1
gastrocnemius recording	4.13	17.4			
Tibial nerve right					
Ankle-AH	3.72	7.0			
Popliteal fossa-ankle	12.1	5.0	45.2	365	8.6
gastrocnemius recording	4.06	10.4			
common peroneal nerve left					
Ankle -EDB	3.79	5.6			
fibular head inferior-ankle	11.3	4.4	41.3	310	7.5
fibular capitulum supra-fibular capitulum	13.7	4.2	41.7	100	2.4
common peroneal nerve left					
Ankle -EDB	3.54	7.3			
fibular head inferior-ankle	10.8	5.2	42.0	305	7.3
fibular capitulum supra-fibular capitulum	13.1	4.8	43.5	100	2.3
Ulnar nerve left					
Wrist -ADM	2.96	14.3			
Below elbow – wrist	6.42	12.9	50.6	175	3.5
Above elbow-below elbow	8.59	12.0	50.7	110	2.2
Axillary - above elbow	10.3	11.7	58.5	100	1.71
Ulnar nerve left					
Wrist -ADM	2.77	14.7			
Below elbow – wrist	6.11	15.1	52.4	175	3.3
Above elbow-below elbow	7.94	15.5	57.4	105	1.83
Axillary - above elbow	9.69	14.4	57.1	100	1.75
Median nerve left					
Wrist-APB	3.73	10.0			
Elbow-wrist	7.58	8.8	55.8	215	3.9
Axillary-elbow	9.88	10.4	56.5	130	2.3
Erb- axillary	14.0	10.6	61.9	255	4.1
Median nerve right					

Wrist-APB	3.96	9.2			
Elbow-wrist	7.90	7.8	54.6	215	3.9
Axillary-elbow	10.1	9.4	59.1	130	2.2
Erb- axillary	14.3	8.7	60.7	255	4.2

B. Sensory Nerve Conduction Studies

Nerve	**Peak Lat (ms)**	**Amp (uV)**	**CV (m/s)**	**Dist (mm)**
Sural nerve left				
Middle calf - lateral malleolus	4.22	1.14	34.4	145
Sural nerve right				
Middle calf - lateral malleolus	3.86	0.44	38.9	150
Ulnar nerve left				
Digital nerve- Wrist	2.95	1.83	40.7	120
Ulnar nerve right				
Digital nerve- Wrist	2.98	1.40	40.3	120
Median nerve left				
Digital nerve II - Wrist	3.06	5.3	49.0	150
Median nerve right				
Digital nerve II - Wrist	3.09	2.9	48.5	150

C. F-Wave

Nerve	**F-M Lat**	**F-Lat**	**M-Lat**	**#F**	
	ms	ms	ms	#	F%
Left tibial nerve Ankle-AH	52.1	56.7	5.3	20.0	100
Right tibial nerve Ankle-AH	50.8	55.3	5.4	20.0	100
Left ulnar nerve Wrist-ADM	26.6	28.6	2.8	20.0	100
Right ulnar nerve Wrist-ADM	26.1	28.5	3.0	20.0	100
Left median nerve Wrist-APB	24.6	27.4	3.7	20.0	100
Right median nerve Wrist-APB	24.8	27.8	3.8	20.0	100

D . EMG MUP Data

	spontaneous potential				amplitude	time limit	Raise phase
	fibrillation	positive phase	fasciculation	CRD	uV	ms	
Left quadriceps	+	++	-	-	1769	16.7	monomiscible
Right quadriceps	-	-	-	-	2475	16.6	monomiscible
Left tibialis anterior	+	++	-	-	1926	16.3	monomiscible
Right tibialis anterior	-	-	-	-	1042	14.1	monomiscible
Right gastrocnemius	-	-	-	-	1100	10.9	monomiscible
Left biceps	-	-	-	-	1047	14.7	monomiscible
Left dorsal interosseous muscle I	-	-	-	-	1619	14.5	monomiscible
Right dorsal interosseous muscle I	-	-	-	-	1966	13.9	monomiscible

Table 3 PD-1 associated nervous system adverse reactions

References	PD-1	Peripheral neuropathy	CNS system			Neuromuscular junction disease	Nonspecific symptom
			Demyelination disease	Encephalitis/myelitis	meningitis		
Feng et al.,2017[11]	Pembro	2		3			
	Nivo		1	2		1	
Larkin et al.,2017[9]	Nivo	22		5	5	3	6
Kao et al.,2017[12]	Pembro	3		1			
	Nivo	1					1
Vitt et al.,2018[13]	Pembro			1			
Sato et al.2019[14]	Pembro	34		20	10	32	
	Nivo	53		26	6	55	
Johnson et al.,2019[5]		64		186	36	197	
Vogrig et al.,2020[15]	Pembro			4	1		1
	Nivo			5	2		1
Kolb et al.,2018[16]	Pembro/ Nivo					2	
Fellner et al.,2018[4]	Pembro	1					
	Nivo	1		3		1	
Zhao et al.,2021[17]	Pembro	4		6			
	Nivo	6		22	2	51	
	Cemi			1			
Xu xiaoting et, 2021[18]	Pembro					1	
Wang weilan et, 2021[19]	toripalimab					1	

Table 4 Oligoclonal band (OCB) typing and clinical significance

Typing	Result	Clinical significance
Type I	OCB was not detected in cerebrospinal fluid and serum	No associated immune disorders had been present.
Type II	OCB was present in cerebrospinal fluid but not in serum	It is commonly seen in multiple sclerosis, autoimmune encephalitis, optic neuromyelitis, and some special infections.
Type III	OCB was present in cerebrospinal fluid and serum, but there was an additional zone in CSF	It is seen in encephalomyelitis, ADEM, acute myelitis and viral encephalitis infected by special pathogens.
Type IV	Identical OCBs in cerebrospinal fluid and serum	It can be seen in patients with inflammatory demyelinating disease of the spinal cord, GBS, and leukemia after transplantation.
Type V	Identical monoclonal bands in cerebrospinal fluid and serum	It usually occurs in some patients with hematological diseases, poems, monoclonal gammaglobulinemia (MGUS) -related peripheral neuropathy

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