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Guillain-Barré Syndrome Related to Pembrolizumab in Metastatic Triple Negative Breast Cancer

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Abstract

Immune Checkpoint Inhibitors (ICIs) are increasingly application in the treatment of advanced cancers these years, exhibiting the potential to be the primary method in oncotherapy. However, with the applying of ICIs, the immune-related Adverse Events (irAEs) were also reported gradually. Here, we reported a 51-year-old female with metastatic Triple Negative Breast Cancer (TNBC) developing into Guillain-Barré Syndrome (GBS) after receiving four months of anti-Programmed cell Death protein 1 (PD-1) antibodies treatment with pembrolizumab and we discussed the diagnose and treatment of GBS related to irAEs.

Keywords: ICI; TNBC; GBS; PD-1

Introduction

PD-1, a cell surface receptor expressed on T lymphocytes, acting as an immune checkpoint biomarker, plays a key role in the cancer therapy. In tumor microenvironment, binding of PD-1 and Programmed cell Death 1 Ligand 1 (PD-L1), expressed mainly by tumor cell, could inhibit the function of cytotoxic T lymphocyte, and result in the escape of tumor cell from immune surveillance by T cells. Under normal status, PD-L1 expressed on the surface of antigen presenting cell, combines with PD-1, triggering the PD-1/PD-L1 signaling and inducing the immune self-tolerance and preventing autoimmune disease [1].

Anti-PD-1 antibodies are increasingly applied in the solid tumor treatment current years. Acting as an immune checkpoint, they might induce autoimmune diseases through unclear mechanisms. Anti-PD-1 antibodies exhibit to be hopefully first line therapy in some specific cancer, but the irAEs had also been reported correspondingly [2]. Nivolumab, and pembrolizumab had been reported to be associated with neurological adverse events [3-5]. Pucotenlimab, a newly PD-1 targeting antibody applied in the treatment of TNBC, exhibits its therapeutic effects [6,7]. We report a case diagnosed as GBS related to pucotenlimab treatment in metastatic TNBC.

Case Presentation

In August 2022, a 51-year-old female who had received pembrolizumab (200 mg, Q3W) for brain metastatic TNBC for 4 months, was admitted to our department with chief complains of acute weakness and numbness combined with pain of both lower limbs for half month. During the course, she suffered from urination defecation. One week before she was admitted, she emerged left facial paralysis and combined with dysphagia. She was fed bad and bedridden. The past medical history was significant for TNBC and she received left breast radical mastectomy in 2019. She denied any fever, diarrhea, vaccination, or any other infectious within at least one month before she was admitted.

Physical examination revealed left-side peripheral facial paralysis, reduced gag reflex, dysarthria, and decreased muscular strength (grade 3/5) and tension, disturbance of sensory and negative tendon reflex of both lower limbs. Babinski signs were negative. Neck was rigid. Muscular strength, tension and sensory of two upper limbs were normal. No sensory level was found. The differential diagnosis of paraplegia was broad. Spinal cord disorders such as myelitis, compression, vascular disease or hemorrhage were suspected firstly, which were the common causes of paraplegia. Given the specific past medical history of TNBC, enlarged metastatic lesion and paraneoplastic syndrome were also take into consideration. Neuropathy such as peripheral neuropathy or GBS should also be distinguished. Although muscular disease and neuromuscular transmission disorder could also result in paralysis of lower limbs, the combination of sensory disorder excluding the possibility of diagnosis.

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Table 1: Electromyogram of two lower limbs.

Motor nerve conduction velocity	Latency period	Amplitude	Distance	Conduction velocity	F-wave latency period
	ms	mv	mm	m/s	ms
Nervus peroneus communis, motor, left					
Ankle to Extensor Digitorum Brevis (EDB)	4.67	1.01	50		NP
Knee to ankle	12.5	1.02	330	37.4	
Nervus peroneus communis, motor, right					
Ankle to Extensor Digitorum Brevis (EDB)	4.27	1.43	50		NP
Knee to ankle	17.7	1.13	330	21.4	

sensory nerve conduction velocity	Latency period	Latency period	Distance	Conduction velocity
	ms	uv	mm	m/s
Nervi peroneus superficialis, sensory, left				
Ankle to dorsum pedis	NP	--		
Nervi peroneus superficialis, sensory, right				
Ankle to dorsum pedis	NP	--		

Left tibial nerve, H Reflex			
	M-Lat	H-Lat	H/M Amp
	ms	ms	-
Knee to gastrocnemius	-	45.6	-

Right tibial nerve, H Reflex			
	M-Lat	H-Lat	H/M Amp
	ms	ms	-
Knee to gastrocnemius	-	42.8	-

MRI of brain and whole spinal cord were performed. Brain MRI showed the metastatic tumor exhibited circle enhancement in the right frontal lobe (Figure 1a), with encephaledema around the lesion (Figure 1b), that could not explain these symptoms. MRI of whole spinal cord showed no corresponding lesions (Figure 1c, 1d), excluding the spinal cord diseases. Electromyogram (Table 1) was performed to differential with peripheral neuropathy. Prolonged latent phase of Compound Muscle Action Potential (CMAP) and H-reflex of the bilateral tibial nerves, negative F-wave, combined with decreased conduction velocity of bilateral common peroneal nerves and loss of Sensory Nerve Action Potential (SNAP) of bilateral superficial peroneal nerve were reported, suggesting the acute injury of nerve root of both lower limbs, indicating the diagnosis of neuropathy. Basic metabolic panel showed decreased sodium (125 mmol/L), chloride (89 mmol/L) concentration suggesting malnutrition caused by dysphagia. Normal potassium concentration (3.53 mmol/L) excluding the diagnosis of periodic paralysis. Complete blood count showed raised leukocyte (12.58×10^9/L) and neutrophils (11.6×10^9/L) combined with elevation of urinary leukocyte (85.05 p/HFF), and leukocyte esterase (+++) suggesting urinary tract infection. Cancer marker revealed elevated CA15-3 (48.65 U/ml), a common marker elevated in metastatic breast cancer, supporting the deterioration of breast cancer. To further worked out the reason of neuropathy, antibodies of neuropathy from serum was tested. The result showed that anti-GM1-IgG and anti-GT1a-IgG were positive, supporting the diagnosis of GBS. Furthermore, the antibodies of paraneoplastic syndrome were also performed and revealed positive of anti-Amphiphysin (AMPH)-IgG, an antibody which is commonly found in breast cancer. We considered that anti-GM1-IgG and anti-GT1a-IgG were the pathogenic antibodies and finally diagnosed the

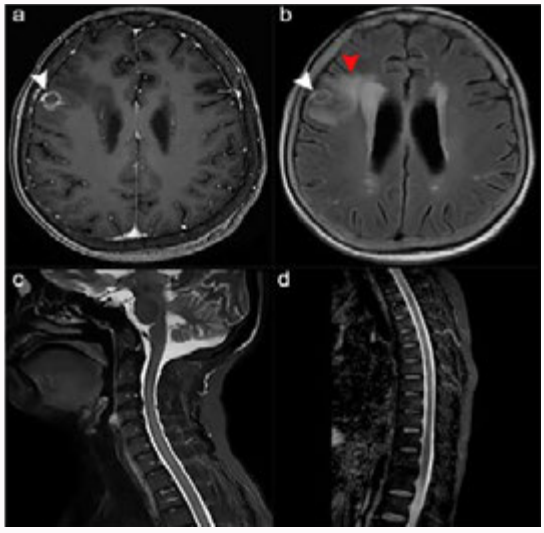

Figure 1: MRI of brain and spinal cord.
(a) Enhanced MRI of brain showed metastatic tumor lesion with ring enhancement in the right frontal lobe in (white arrowhead). (b)T2WI showed metastatic lesion (white arrowhead) with encephaledema around the lesion (red arrowhead). (c, d) MRI of the cervical, thoracic and lumbar spinal cord exhibited no obvious abnormality.

patient as GBS attributed to irAEs.

For the treatment, intravenous immunoglobulin (IVIg, 0.4 g/kg/d) was prescribed for 5 days, following by methylprednisolone (500 mg/d i.v.) for another 3 days. During the treatment, mannitol, glycerin fructose, furosemide and albumin were also given to counteract the intracranial hypertension. The patient got shortly palliated but gradually developed into respiratory failure and she was transferred to intensive care unit.

Discussion

Many anti-PD-1 antibodies, such as nivolumab and pembrolizumab, have been applied in the treatment of unresectable or metastatic tumors such as melanoma, non-small cell lung cancer and so on. However, with the increasing application of ICIs in cancer treatment, irAEs have been reported in clinical studies. IrAEs can involve such as nervous system (irAE-N), respiratory system, musculoskeletal system, cardiac system and others [8]. The mechanisms of irAEs are still not fully revealed, which involves the breakdown of self-tolerance mediated by T and B lymphocyte, autoantibodies and cytokines [9]. Among these irAEs, although rare, the neurological complications related to ICIs have been sporadically documented [2].

Pucotenlimab, a newly rose humanized anti-PD-1 antagonist IgG4 mAb, was applied into the treatment of advanced solid tumors in the clinical trials currently. The neurologic complications have also been reported following up its applied in the clinical trials. We reported a GBS patient related to the treatment of pucotenlimab in TNBC. Based on the diagnosis of GBS related to ICIs, we followed the approaches of irAE-N and general guidance statements recommended by the consensus [10]. The patient newly developed weakness and numbness of both two lower extremities combined with left peripheral facial paralysis, dysphagia, and urination and defecation disorders within 6 months after starting ICIs (four months after the first application), consistent with the consensus recommendation [10]. Combining with the results of electrodiagnostic studies, blood serum ganglioside antibodies and MRI of brain and spinal cord, we considered the diagnosis of GBS, a syndrome affected peripheral nervous system, which could be classified into Acute Inflammatory Demyelinative Polyradiculoneuropathy (AIDP). According to the guideline, the toxic severity of the ICIs could be classified into G3-G4 [11]. Although the lumbar puncture was not performed in consideration of the intracranial hypertension reflected by stiffness of the neck, and the patient denied a history of infection and diarrhea before the GBS onset, we diagnosed her as GBS related to irAEs rather than idiopathic according to the consensus [10].

As for the treatment of irAE related to irAEs, glucocorticoid was reported to be the first line treatment in the earlier years [2]. IVIg and plasmapheresis could also be applied when the curative effect of glucocorticoid alone was not significant [2]. However, recent updated guideline recommends IVIg or plasmapheresis prior to the corticosteroids [11]. In addition, we should also be aware of the respiratory muscle paralysis caused by GBS, which is lethal as this patient did and mechanical ventilation is usually required.

Interestingly, the paraneoplastic syndrome autoantibody test revealed anti-AMPH-IgG was also positive of this patient. Anti-AMPH-IgG autoantibody is usually associated with stiff-person syndrome accompanied by breast cancer, lung cancer or melanoma [12,13]. Tumor patients with Anti-AMPH-IgG autoantibody could also exhibit paraplegia which might be diagnosed as paraneoplastic myelopathy or neuropathy [14]. As for this patient, we deduced that anti-GM1-IgG and anti-GT1a-IgG were the pathogenic antibodies according to the acute disease course, and anti-AMPH-IgG was the autoantibody combined with the primary breast cancer.

Conclusion

In conclusion, for patients with cancer and receiving ICIs treatment, developing into weakness and (or) numbness in extremities, combined with any dysphagia, facial weakness, and dyspnea, the diagnosis of neurological irAE, especially GBS should be aware of. According to the updated guideline in 2021, the therapy of standard dose of IVIg or plasmapheresis is preferentially recommended in the treatment of GBS related to ICIs. Moreover, glucocorticoids were also recommended, which is different from idiopathic GBS.

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