Neurological Adverse Events Induced by Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Current Perspectives and New Development

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ABSTRACT: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of multiple malignancies, especially in non-small cell lung cancer (NSCLC). With the extensive application of ICIs in clinical practice, clinicians have to manage their toxicities, which are often termed immune-related adverse events (irAEs). Several ICIs, such as nivolumab, pembrolizumab, atezolizumab, and durvalumab, have been approved by the US Food and Drug Administration (FDA) to treat advanced NSCLC, accompanied by a broad spectrum of toxicity reactions. However, ICI-associated neurological toxicities, including polyneuropathy, Bell palsy, encephalopathy, and myasthenia gravis, have not been well recognized, present a challenge for clinicians to improve awareness of supervision, recognition, and management before death from them. Herein, we have summarized the incidence, diagnosis, clinical manifestations, potential mechanisms, treatments, and outcomes of ICI-related neurotoxicity and optimized the management approach for NSCLC patients. Prompt recognition and proper management are indispensable to reduce the morbidity of these patients with immune-related neurological toxicities.

KEYWORDS: Immune checkpoint inhibitors, neurotoxicity, polyneuropathy, myasthenia gravis, encephalopathy, Guillain-Barre syndrome, non-small cell lung cancer

Introduction

Lung cancer has been regarded as 1 of the most common cancers with both high incidence and mortality worldwide.1 Among them, non-small cell lung cancer (NSCLC) comprises a high incidence of more than 85%.2 However, nearly all patients treated with traditional chemotherapy and radiotherapy, and the molecular targeting agents will display disease progression due to acquired resistance, which is inevitable.3 Cancer immunotherapy, arising vigorously after 2000, is a remedial modality that exploits the immune system to recognize, target, and eliminate cancer cells.4 Immune checkpoint inhibitors (ICIs), mainly composed of programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibodies (mAbs), have been proved effective toward numerous targets and efficaciously inhibit the PD-1/PD-L1 and CTLA-4 pathways.

Immune-related adverse events (irAEs) in patients with NSCLC and multiple organs and numerous systems. The most common irAEs documented from clinical trials include rash, pruritis, thyroiditis, autoimmune hypophysitis, pneumonitis, colitis, and hepatitis.8 Moreover, some less common irAEs have also been reported, including cardio toxicity, ocular toxicity, and neuromyotoxicity.9 Among all these adverse effects, ICI-related neurological toxicities are rare, which may lead to the permanent interruption of therapeutic regimen, treatment of corticosteroids, exacerbation of cancers, or even death. To date, as the case reports have documented various ICI-related neurotoxicity in patients with NSCLC, a safety profile of ICIs needs to be consummated, and the incidence of neurotoxicity needs to be adequately assessed.8 Our review collected 20 case reports of ICI-related neurological adverse events (NAEs) in patients with NSCLC and recorded their NAE types, symptoms, treatments, and outcomes (Table 1). Multiple accessory examinations are essential in the early identification of these toxicities and are summarized (Table 2).

We select the 4 most common NAEs based on case reports assembled and summarize their incidence, potential mechanisms, diagnosis, treatment, and several notable questions of various types of ICI-related neurological toxicities.
| REFERENCE | CASE REPORT/SERIES | AGE/SEX | CANCER HISTOLOGICAL CLASSIFICATION/STAGE | ICI DRUGS/DOSAGE | TIME OF ONSET/TIME TO EVENT | SYMPTOMS | NEUROLOGICAL ADVERSE EVENTS | WITHDRAW THE DRUG | TREATMENT/DRUGS/DOSAGE | THE TIME OF RECOVERY | CTCAE GRADE | OUTCOME |
|-----------|-------------------|---------|------------------------------------------|-----------------|-----------------------------|----------|------------------------------|------------------|--------------------------|----------------------|-------------|---------|
| 10        | Abe et al         | 58/M    | Lung adenocarcinoma/recurrent stage      | Nivolumab       | Within 1 week               | Irritated, fidgety, communicative disorders, compulsive sequential movements | Akathisia   | YES                        | Oral prednisolone, one pulse methylprednisolone, oral and IV sedative drugs | NR           | 2       | Failed to relieve his symptoms |
| 11        | Richard et al     | 74/M    | Squamous NSCLC/stage IV                 | Nivolumab       | Within 1 week               | Gradual decrease in mental status, repeated fall, mumbling, inability to follow commands and stand on his own intuition, agitated, confused, visual hallucinations | Encephalitis | NO                        | IV decadron, IV Solu-Medrol, oral steroid               | NR           | 2       | Improved after 6-week steroid taper |
| 12        | Nakatani et al    | 73/F    | Squamous cell lung cancer/stage IV      | Nivolumab       | 20 weeks later              | Ptosis, lower limb weakness, photophobia | Lambert-Eaton myasthenic syndrome | YES            | Anticholinesterase inhibitors, oral prednisolone, pyridostigmine, anti-acetylcholinesterase inhibitors | 115 weeks later | 2       | Stable |
| 13        | Schneider et al   | 78/M    | Squamous cell lung cancer/stage IV      | Nivolumab       | 28 weeks later              | Apathy, aphasia, withdrawal from pain and verbal response, paresis of the left facial nerve | Autoimmune encephalitis | YES           | Antiepileptic treatment, intravenous methylprednisolone | 60 weeks later | 3-4     | Improved |
| 14        | Lettinger et al   | 67/F    | Squamous cell lung cancer/stage IV      | Nivolumab       | 2 weeks later               | Seizures, dyspnea, fear, confusion, fluent aphasia, perseveration, disorientation, speech arrest, cannot execute complex request | Necrotizing encephalopathy | YES           | IV methylprednisolone, immunoglobulins, antiviral treatment, antiepileptic treatment | NR           | 5       | Died (8 weeks later) |
| 15        | Jacob et al       | 68/F    | Squamous cell lung cancer/stage IV      | Nivolumab       | 13 weeks later              | Fatigue, loss of motor and sensory function in arms and legs, respiratory muscle paralysis | Guillain-Barre syndrome | YES           | Ventilator support, IVlg, plasma exchange | NR           | 5       | Died (15 weeks later) |
| 16        | Läubli et al      | 53/M    | Lung adenocarcinoma/stage IV            | Nivolumab       | NR                          | Progressive gait disturbance, speech difficulties | Cerebral vasculitis/necrotizing encephalitis | YES           | Steroids, excision of the intracranial lesion | NR           | 2       | Improved after excision of the lesion |
| 17        | Fukumoto et al    | 66/M    | NSCLC/stage IV                          | Nivolumab       | 3 weeks later               | Muscle weakness of the lower limbs, became bed-bound | Acute demyelinating polyneuropathy | YES           | Steroids, IVlg | 17 weeks later | 3-4     | Improved |
| 18        | Tan et al         | 45/M    | NSCLC/advanced stage                    | Nivolumab       | 2 weeks later               | Exertional dyspnea, ptosis, and ophthalmoplegia | Myasthenic crisis and myositis | YES           | Pyridostigmine, methylprednisolone, immune globulin, intubation | 24 weeks later | 3-4     | Improved |

(Continued)
| Reference | Age/Sex | Cancer, Histological Classification, Stage | ICI Drugs/Dosage | Time of Onset/Time to Event | Symptoms | Neurological Adverse Events | Withdraw the Drug | Treatment/Drugs/Dosage | Time of Recovery | CTCAE Grade | Outcome |
|-----------|---------|-----------------------------------------|----------------|-----------------------------|-----------|----------------------------|-----------------|------------------------|----------------|-------------|---------|
| 19        | Chen et al | 57/M | Squamous cell lung cancer, stage IV | Ipilimumab and nivolumab | 4 weeks later | Ptosis, dyspnea, and muscle weakness | Myasthenia gravis | NO | IV steroids, oral pyridostigmine | NR | 2 | Improved but died because of hospital-acquired pneumonia |
| 20        | Chen et al | 65/M | Squamous cell lung cancer, stage IIIIB, cT4aN2M0 | Nivolumab | 5 weeks later | Weakness of 4 extremities, ptosis, limited eye movement, dropped head, drooling with dysphagia, respiratory failure | Myasthenia gravis | YES | Oral steroids and pyridostigmine | NR | 5 | Died (9 weeks later) |
| 21        | Ong et al | 68/M | Lung adenocarcinoma, stage IV | Pembrolizumab | 4 weeks later | Paresthesia, limb and facial weakness | Guillain-Barré-like syndrome | YES | Intravenous steroids, IVlg | 12 weeks later | 2 | Improved |
| 22        | Polat et al | 65/M | NSCLC, stage IV | Nivolumab | 4 weeks later | Blurry vision, ptosis, and intermittent diplopia | Myasthenia gravis | YES | Pyridostigmine | 20 weeks later | 2 | Improved |
| 23        | Sciacca et al | 81/M | Lung adenocarcinoma, stage IV | Nivolumab | 4 weeks later | Bilateral ptosis, nasal speech, and proximal limb weakness | Myasthenia gravis | YES | Oral steroids | 8 weeks later | 2 | Improved |
| 24        | Hussein et al | 47/F | Poorly differentiated lung cancer, neuroendocrine features, stage IV | Nivolumab | 5 weeks later | Nausea, vomiting, disorientation, generalized tonic clonic seizure | PRES | YES | Treated with supportive therapy | NR | 2 | Improved |
| 25        | Hibino et al | 83/M | Squamous cell lung cancer, stage IV, cT1cN3M1c | Pembrolizumab | 5 weeks later | Easy fatigability of the eyelids and eye movement, bilateral ptosis, diplopia, posterior neck myalgia, neck extensor weakness | Myasthenia gravis with myositis | YES | Oral steroids, pyridostigmine | 14 weeks later | 2 | Improved |
| 26        | Mori et al | 64/M | NSCLC, stage IV | Atezolizumab | 48 weeks later | Sudden visual loss | Optic neuritis | YES | IV methylprednisolone 1g for 3 days, then 30 mg PO prednisolone administration | NR | 2 | Improved |
| 27        | Narumi et al | 75/M | Lung squamous cell carcinoma, stage IIIA, T3N1M0 | Nivolumab | 8 weeks later | Acute paralysis in bilateral lower limbs, sensory loss below Th10 level, urinary retention | NMOSD | YES | Steroid pulse therapy, plasmapheresis | 34 weeks later | 3-4 | Improved |
| 28        | Horio et al | 63/M | Lung adenocarcinoma, stage IVB, cT1cN3M1c | Pembrolizumab | Within 1 week | Homonymous hemianopia | Trousseau syndrome | NO | Unfractionated heparin | NR | 5 | Improved but died because of hemorrhagic infarctions |
| 29        | Tan et al | 66/M | Metastatic NSCLC | Atezolizumab | 12 weeks later | Ataxic wide-based gait | Cerebellar ataxia | YES | Prednisolone 1mg/kg | NR | 2 | Improved |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor; IV, intravenous; IVlg, intravenous immunoglobulin; NMOSD, neuromyelitis optica spectrum disorder; NR, not reference; NSCLC, non-small-cell lung cancer; PO, oral; PRES, posterior reversible encephalopathy syndrome.
Table 2. Laboratorial, electrophysiological, and imaging examinations of ICI–related neurological adverse events in NSCLC.

| REFERENCE | AGE/SEX | NEUROLOGICAL ADVERSE EVENTS | EEG/EMG/SFEMG | NCS | RNS | IMAGE EXAMINATION | ANTIBODIES OF PARANEOPLASTIC NEUROLOGICAL SYNDROME/SEUM LABORATORY DATA | CSF TEST | CO-OCCURRING NON-NEUROLOGICAL IAEs |
|-----------|---------|-----------------------------|----------------|-----|-----|-------------------|-----------------------------------------------------------------------|---------|-----------------------------------|
| Abe et al | 58/M Akathisia | NR | NR | NR | Brain MRI: negative | Negative for all | Negative | NO |
| Richard et al | 74/M Encephalitis | EEG: mild slowing, no evidence of seizure activity | NR | NR | Chest X ray: negative MRS: not conducted | Not conducted | Negative | Euthyroid sick syndrome |
| Nakatani et al | 73/F Lambert-Eaton myasthenic syndrome | NR | Low-amplitude CMAP | Waning phenomenon in 3 Hz RNS, waxing phenomenon in 10 and 20 Hz RNS | Chest CT: right hilar lymphadenopathy, primary tumor in the right lower lobe | AChRAbs: negative, anti-P/Q-type VGCC antibody: positive, anti-thyroglobulin antibody: positive | Negative | Hypothyroidism |
| Schneider et al | 78/M Autoimmune encephalitis | EEG: moderate background slowing, focal delta slowing over the left temporal region | NR | NR | CT: negative Brain MRI: negative | Negative for all | Reduced level of glucose, elevated lactate: 4.1 mmol/L, protein level: 1027 mg/L, pleocytosis: 16 lymphocytes/µL | NO |
| Leitinger et al | 67/F Necrotizing encephalopathy | EEG: rule out complex partial status epilepticus, moderate diffuse slowing | NR | NR | MRI: edematous disseminated lesions | Negative for all | Inflammatory CSF findings and increased IgG level | NO |
| Jacob et al | 68/F GBS | NR | NR | NR | Brain CT: partial response Spine MRI: negative | | | |
| Läubli et al | 53/M Cerebral vasculitis/ necrotizing encephalitis | NR | NR | NR | Brain MRI: new parietotemporal lesion in proximity of the formerly irradiated masses | Antibodies against neuronal antigens: negative, anti-SSA/Ro and anti-SSB/La antibodies: positive | | NO |

(Continued)
| Reference        | Age/ Sex | Neurological Adverse Events | EEG/EMG/ SFEMG | NCS | RNS | Image Examination | Antibodies of Paraneoplastic Neurological Syndrome/Serum Laboratory Data | CSF Test | CO-Occurring Non-Neurological IRAEs |
|------------------|----------|-----------------------------|----------------|-----|-----|-------------------|-------------------------------------------------------------------------|----------|----------------------------------|
| Fukumoto et al²⁷| 66/M     | Acute demyelinating polyneuropathy | NR             | NR  | NR  | IgM antibodies to GM2 and GalNAc-GD1a: positive, CK: 36 IU/L | CSF: 4 leucocytes/μL, protein level: 339 mg/dL | NO       |                                  |
| Tan et al¹⁸      | 45/M     | Myasthenic crisis and myositis | NR             | NR  | No decremental response | Brain MRI: no evidence of stroke or metastasis                     | AChR Abs: 2.00 nmol/L, CK: 2682 U/L | NR       | NO                               |
| Chen¹⁹           | 57/M     | Myasthenia gravis, myositis, and polyneuropathy | EMG: active denervation and myopathic changes in sample muscles, SFEMG over right orbicularis oculi mean consecutive difference of 74 µs | No decremental response | NR | AChR Abs: 0.70 nmol/L, CK: 2682 U/L | Slightly lower protein level at 13 mg/dL | NO       |                                  |
| Chen et al²⁰     | 65/M     | Myasthenia gravis            | EMG: negative  | Negative | Brain MRI: negative | AChR Abs: not detected, CK: 2216 U/L, AST: 153 U/L, ALT: 110 U/L, LDH: 484 U/L, troponin-I: 2.62 ng/mL | NR       | NO                               |
| Ong et al²¹      | 68/M     | Guillain-Barré-like syndrome | NR             | Prolonged tibial motor distal latency, partial conduction block in peroneal motor nerves, sparing of the sural sensory response | NR | Spine MRI: degenerative changes | Paraneoplastic autoantibodies: negative | NR       | NO                               |
| Polat et al²²    | 65/M     | Myasthenia gravis            | NR             | Normal after the treatment of pyridostigmine | Normal after the treatment of pyridostigmine | MRI: negative Chest X ray: negative | AChR Abs and anti-MUSK: negative after myasthenia gravis disappear | NR       | NO                               |
| Sciaccia et al²³ | 81/M     | Myasthenia gravis            | SFEMG over orbicularis oculi abnormal (mean jitter, 36 µs; 15% pairs with abnormal jitter) | NR | Negative | AChR Abs: 0.40 nmol/L, ALT: 296 U/L, AST: 325 U/L | NR       | NO                               |

(Continued)
**Table 2. (Continued)**

| REFERENCE   | AGE/SEX | NEUROLOGICAL ADVERSE EVENTS | EEG/EMG/SFEMG | NCS | RNS | IMAGE EXAMINATION | ANTIBODIES OF PARANEOPLASTIC NEUROLOGICAL SYNDROME/SERUM LABORATORY DATA | CSF TEST | CO-OCCURRING NON-NEUROLOGICAL IRAES |
|-------------|---------|-----------------------------|----------------|-----|-----|-------------------|--------------------------------------------------------------------------|----------|-----------------------------------|
| Hussein et al<sup>24</sup> | 47/F    | PRES                        | NR             | NR  | NR  | MRI: PRES         | Negative                                                                  | MRI: PRES | NO                               |
| Hibino et al<sup>25</sup> | 83/M    | Myasthenia gravis with myositis | NR             | NR  | Negative | Brain MRI and abdominal CT: negative | Autoimmune antibodies: negative, CK-4361 IU/L, aldolase: 134.8 IU/L, myoglobin: 4572.0 ng/mL, LDH: 580 IU/L, AST: 269 IU/L, ALT: 222 IU/L | MRI: PRES | Myositis and hepatitis. |
| Mori et al<sup>26</sup>   | 64/M    | Optic neuritis              | NR             | NR  | NR  | MRI: high-intensity lesion in left optic nerve | Negative | Protein level: 69 mg/dL | Hypopituitarism               |
| Narumi et al<sup>27</sup> | 75/M    | NMOSD                        | NR             | NR  | NR  | Spinal MRI: hyperintense lesions between C5-6 and Th12-L1 | Paraneoplastic autoantibodies: negative, AQP4 antibody: positive | WBC: 1195 IU/L, protein level: 380.9 mg/dL, glucose concentration: 40 mg/dL | NO                               |
| Horio et al<sup>28</sup>  | 63/M    | Trousseau syndrome          | NR             | NR  | NR  | Brain MRI: intratumor hemorrhage, small infarct near tumor, multiple cerebral infarcts | Negative | Brain hemorrhagic infarction |
| Tan et al<sup>29</sup>    | 66/M    | Cerebellar ataxia           | NR             | NR  | NR  | Brain CT: negative Brain MRI: small vessel disease | Negative | Negative | NO                               |

Abbreviations: AChR Abs, anti-acetylcholine receptor antibodies; ALT, alanine aminotransferase; AQP4, aquaporin 4; AST, aspartate aminotransferase; CK, creatine kinase; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalograph; EMG, electromyograph; GBS, Guillain-Barré syndrome; LDH, lactate dehydrogenase; MRI, magnetic resonance image; MUSK, muscle-specific tyrosine kinase; NCS, nerve conduction study; NMOSD, neuromyelitis optica spectrum disorder; NR, not reference; NSCLC, non-small cell lung cancer; PRES, posterior reversible encephalopathy syndrome; RNS, repetitive nerve stimulation; SFEMG, single-fiber electromyography; VGCC, voltage-gated calcium channel; WBC, white blood cell.
Incidence of NAEs

To date, due to the lower incidence of ICI-related NAEs, data available on it in clinical trials of NSCLC are limited, and most of these adverse effects are documented in case reports. Although ICI-related NAEs are relatively rare, approximately accounting for 1% to 3% of all irAEs in monotherapies, they may strongly affect the prognosis and even lead to patients’ death with cancers. Different groups of statistics confine the incidence of immune-related neurotoxicity in ipilimumab-treated patients to 1% to 1.6%, and anti-PD-1 agents (nivolumab + pembrolizumab) to 3% to 3.2%. This rate can be much higher with combined ICIs, surpassing 10%. It has been estimated that within 9208 patients distributed in 59 trials, the incidence of ICI-related NAEs in combined therapy (nivolumab + ipilimumab) is up to 12%. Researchers based on NSCLC patients rarely document ICI-related neurological effects. Based on the data available in a multicenter analysis, we discover the incidence of nivolumab-related neurological toxicities in 1.3% (3/230) and pembrolizumab in 0% (0/41). In another retrospective research of 134 NSCLC patients, ICI-related neurological toxicities have been associated with nivolumab. Neurological toxicities only manifest as myasthenia gravis (MG), which happens to only 1 patient, indicating an incidence of 0.7%. Besides, a retrospective study with a large sample size of patients with NSCLC only indicates a gross incidence of anti-PD-1-related neuromuscular diseases, rheumatisms, fever, anorexia, pancreatitis, and asthenia.

The occurrence of neurological toxicities can happen in any progress of applications of ICIs, which ranges widely from soon after the first dose to a prolonged period after the cessation of drugs. The length of time to occurrence relies on the medical history, categories of drug application, and applied dosages of drugs. Based on a retrospective study in a tertiary-care center, a vast majority of patients (89%) first run into ICI-related neurological toxicities within 12 weeks. According to the case reports we summarize, most ICI-related neurological toxicities occur 1 to 5 weeks after the first dose of administration (Figure 1). However, some cases indicate a relatively rare latter occurrence of neurological toxicities, surpassing 20 weeks after the initiation of ICIs (Figure 1). Late-emerging irAEs have been noticed in long-term responders to PD-1/PD-L1 checkpoint inhibitors. A systematic review also reported that early and late ICI-related encephalitis were possible. In addition, not all irAEs will disappear when antitumor treatment is stopped; some late-irAEs could occur a year after first application. Interestingly, a multicenter study identified that neurological late-irAEs are the only type of irAEs which tends to occur late (>12 months) rather than early (<12 months) in melanoma and NSCLC patients. In this condition, any suspicious symptoms occurring during medication should be noticed even after a long time of drug withdrawal. Wide ranges of time in neurological toxicity initiation possibly augment clinicians’ difficulties in detecting and diagnosing ICI-related NAEs.

![Figure 1. Time to onset of immune checkpoint inhibitor–associated NAEs.](image-url)
Potential Mechanisms of irAEs

Although the development of immunotherapy thrives, the mechanisms of irAEs remain unclear. According to the existing knowledge, the fundamental principles are an imbalance between autoimmunity and immune tolerance, together with an uncontrolled infiltration of inflammatory T cells, production of autoimmune antibodies, and the assembly of cytokines.44

Immune checkpoints are molecules expressed on the surface of cells, acting as immune regulators to maintain immune tolerance and limit autoimmunity. PD-1 and cytotoxic T lymphocyte-associated antigen (CTLA-4) are 2 of the most significant receptors that existed on the surface of cytotoxic T cells, binding their ligands of PD-L1/L2 and CD80/86, reducing Akt activation, thus inhibiting the cytokine and protein synthesis, glucose uptake, prohibiting T-cell activation and proliferation.43,45 It has been proved that blockade of PD-1 and CTLA-4 pathways influences the induction of tolerance of peripheral CD4+ T cell, disrupting the homeostasis of peripheral tolerance.46-49

The specific mechanisms of ICI-related NAEs remain unknown. However, the existence of autoantibodies detected in the serum of patients with ICI-related NAEs provides a potential assumption. Most antigens to autoantibodies detected in the serum of patients with autoimmune neurological toxicities could be identified in nearly all tumor cells called cross-presentation of onconeural antigens.50 Researchers have identified various common antigens expressed in tumor cells and neurons in patients with paraneoplastic neurological syndromes.51-55

The ligand of anti-Hu (ANNA-1) is expressed on the nucleus of all neurons and tumor cells of patients with neurological syndromes in prostate cancer, NSCLC, and neuroblastoma.55-57 Similarly, genes coding for P/Q type voltage-gated calcium channel (VGCC) has been identified, which express both on the presynaptic membrane and cells of lung carcinomas after the treatment of ICIs.53 With the application of ICIs, hyperactivation of the immune system leads to the attack of autoantibodies to self-antigen expressed inside or on the surface of neurons, disrupting linkage between neuromuscular transmission, influencing normal neuronal functions.30,58

In addition to the autoimmune attack to cross-presentation onconeural antigens, it is noteworthy that PD-1 and its ligands are not only expressed on hematopoietic cells but also on a vast majority of cell lines, including pancreatic islet cells, epithelial cells, reticular cells, vascular endothelial cells, and neurons.54,60 It is considering about nervous system, targets of ICI distributed in distinct densities in different anatomical regions. Researches point out that PD-1 is transcribed across the central nervous system, especially the basal ganglia and cortex.61,62 However, CTLA-4 is mostly expressed in the spinal cord and brainstem.62 In this condition, the “off-target” effects of PD-1/PD-L1 and CTLA-4 mAbs could be understood.

Despite the cross-presentations of onconeural antigens, another theory called “epitope spreading” (ES) appears on the scene.63 In the process of tissue dissociation when applying ICIs, tumor cells, together with disrupted nontumor antigens, will release secondary antigens, evoking an expanded immune response. Unlike the primary response, secondary antigens are delivered by antigen-presenting cells near the dissolved tissue, prime T and B cells, and mediating autoimmune response. This potential theory has been mentioned in the applications of CTLA-4 and PD-1/PD-L1 blockade. However, the specificity of it to the nervous system needs to be further explored.63-65

Categories of ICIs-Related Neurological Toxicities

Immune checkpoint inhibitor–related neurological toxicities have various manifestations, which affect the central nervous system or peripheral nervous system. It is estimated that the peripheral nervous system is often affected twice as the central nervous system.66 The manifestations of ICI-related NAEs in the central nervous system include cerebellitis,67 meningitis, encephalitis,68 posterior reversible encephalopathy syndrome (PRES),69 transverse myelitis,70 cerebral vasculitis,71 and multiple sclerosis.71 In the peripheral nervous system, chronic immune demyelinating polyneuropathy (acute inflammatory demyelinating polyneuropathy [AIDP]),72 facial nerve palsy,73 Guillain-Barré syndrome (GBS), Tolosa–Hunt syndrome,32 MG,30 and Lambert–Eaton myasthenic syndrome (LEMS)30 could also be observed.

Encephalitis

Encephalitis is a neurological inflammatory disorder induced by various possible reasons with complex diagnoses.68 Immune checkpoint inhibitor–related encephalitis can occur during any drug administration cycle, and it is estimated to account for 0.1% to 1% of all irAEs in patients with PD-1/PD-L1 monotherapy.13 Patients with ICI-related encephalitis often have a fever, headache, fatigue, working memory loss, altered mental status (consciousness or personality), psychiatric symptoms, and stiff neck.45 It has been documented in 2 cases that encephalitis occurred within 1 week after the first dose of ICI in patients with metastatic NSCLC, and melanoma.74 In NSCLC, initial symptoms appear in a 74-year-old man within 1 week, while in another 78-year-old man, 12 days after the 14th application of nivolumab, he suffers tonic convolution of his right hand and becomes apathy and aphasia.13,35 In this situation, diagnosis should be made as soon as possible. Doctors should first evaluate the Glasgow Coma Scale score and perform a physical examination to assess the patient’s state of consciousness as well as the existence of pathological reflexes.31 Magnetic resonance imaging (MRI) of the brain could suggest encephalitis features, which appear as the hyperintense focus on T2 fluid-attenuated inversion recovery confined to unilateral or bilateral medial temporal lobes or scattered to gray or white matter. Indications of electrocardiograph (ECG) are nonspecific, which adjusts to an electroencephalograph (EEG) as well. The EEG rarely shows specific manifestations. Most are unspecific moderate
background slowing and focal delta slowing. However, its sensitivity is relatively high in the case reports we collected (Figure 2). Research claims that only anti-N-methyl D-aspartate (NMDA) receptor encephalitis has a specific extreme delta brush, which helps diagnose. Adjuvant investigations should be done to exclude diseases that mimic the symptoms, including detailed medical history, laboratory analysis of blood and cerebrospinal fluid (CSF), complete physical and neurological examination, MRI including diffusion-weighted imaging (DWI), and serological autoantibodies. The most common differential diagnosis of autoimmune encephalitis is herpes simplex virus encephalitis. What is difficult for differentiating is the polymerase chain reaction (PCR) result of HSV in CSF may be harmful when it is done too early. A repetitive test should be done until the disease is ascertained. Considering treatments, if the patient is suspected epileptic or in the postictal state, antiepileptic drugs (levetiracetam, midazolam, lamotrigine) should be administrated. Steroidal treatment indicates its effectiveness in ICI-related encephalitis. Corticosteroids, for instance, methylprednisolone, can be administered intravenously or orally according to the severity of symptoms. Anti-infectious treatment should be preventively used.

**Myasthenia Gravis**

Immune checkpoint inhibitor–related MG is a postsynaptic disorder in neuromuscular junctions, which shares its idiopathic modality. It is reported to be the most common neuromuscular disorder in PD-1 inhibitor-related NAEs. Based on the data collected from case reports and retrospective clinical databases, nivolumab-induced MG occupies 21%, whereas pembrolizumab accounts for 33% in patients with all kinds of neuromuscular disorders. The MG onset occurs early after the administration of ICIs in patients with NSCLC, mostly following the first to third cycles. Based on the 6 case reports we summarized in NSCLC, all the patients develop their symptoms within 8 weeks (4 cycles). Among which, 66.7% (4/6) patients suffer symptoms within 4 weeks. The ICI-related MG could affect muscles throughout the whole body. Ocular, bulbar, facial, respiratory muscles, and working muscles of limb and neck are most frequently affected. Clinical manifestations always cover fatigue, blurry visions, bilateral ptosis, diplopia, nasal speech, dysphagia, dysarthria, mild/severe dyspnea, and weakness of limbs. Thorough workups are necessary for the diagnosis of MG. Neurological examination is the fundamental workup that should be done first, including Jolly, Icepack, and Tensilon. Doctors could verify the weakness of specific muscle groups and can further classify the strength them. Low-frequency repetitive nerve stimulation (RNS) is the most common electrophysiological examination conducted in neuromuscular-transmitted disease. Aberrant RNS displays a decrement or decrease in compound muscle action potential (CMAP) amplitude in generalized MG, the detection rate of which is 75%. However, in 6 ICI-related MG patients with NSCLC, 5 are negative, indicating a relatively low sensitivity. Nerve conduction study (NCS) could also assist in diagnosing, indicating the denervation or degeneration in ICI-related patients with NSCLC, but it is unremarkable on most occasions. Single-fiber electromyography (SFEMG) over proper muscles may indicate abnormal jitters in 95% to 99% of patients with MG, similar to ICI-induced MG. However, the specificity of abnormal jitters is relatively low, as it also appears in other muscular or neural diseases. The sensitivity of serological studies in AchR antibodies is higher than RNS, approximately up to 85% in generalized MG. Under this circumstance, the concentration of AchR antibody needs to be measured. The

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**Figure 2.** Summarized a variety of diagnostic results in published case reports. Diagnostic approaches include EEG/EMG/SFEMG, NCS, RNS, image examinations, serological autoantibodies, CK, ALT/AST, and CSF. White blocks mean this examination has not been mentioned in case reports; green blocks represent negative results; red blocks represent positive results. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CSF, cerebrospinal fluid; EEG, electroencephalograph; EMG, electromyograph; ICI, immune checkpoint inhibitor; NAEs, neurological adverse events; NCS, nerve conduction study; RNS, repetitive nerve stimulation; SFEMG, single-fiber electromyography.
ICI-induced patients with NSCLC.20,25 abnormally increased CK, overwhelming several times of upper limit in creatine kinase (CK) chemistry examination, always indicates muscular weakness within a few days.86 Plasmapheresis could reduce therapeutic efficacy. mapheresis and IV immunoglobulin (IVIg) will relieve their symptoms. Patients with NSCLC who have severe ICI-related MG, plasmapheresis alone is not sufficient. After completing the treatment cycle, 92 the most remarkable improvement occurs, ranging from 4 weeks of ICI application to several months.93-95 However, the incidence of ICI-related GBS in patients with NSCLC has not been reported alone. Compared to MG, the onset time of ICI-related GBS is more variable, with 3% to 10% of patients with NSCLC could acquire partial relief or complete remission after multiple treatments to ICI-related MG.19,20,22,23,25

The prior treatment to ICI-induced MG is withdrawing or lowering the dose of ICI, which should be individualized according to its severity. After the cessation of ICI, patients with MG will acquire great improvement.33 Under this circumstance, the cholinesterase inhibitors (pyridostigmine bromide), a first-line therapy for MG, is recommended in 30 to 90 mg 3 times a day.22,77 It is noteworthy that overdose of pyridostigmine bromide prolongs depolarization and exacerbates muscular weakness, resulting in a cholinergic crisis. In addition, corticosteroids are mostly administered and recommended in ICI-related MG, which are applied with or after cholinesterase inhibitors.18,19,25,77 When the symptoms cannot be appropriately controlled by monotherapy of pyridostigmine bromide, IV prednisone (0.75-1.00 mg/kg/d) could be tapered gradually to oral steroids in patients with improved symptoms.25,89 Patients with NSCLC who have severe ICI-related MG, plasmapheresis and IV immunoglobulin (IVIg) will relieve their muscular weakness within a few days.86 Plasmapheresis could rapidly decrease serological autoantibodies concentration while IVIg could competitively bind to the Fc receptors. Most patients with NSCLC could acquire partial relief or complete remission after multiple treatments to ICI-related MG.19,20,22,23,25

Guillain-Barré Syndrome
Guillain-Barré syndrome is an autoimmune-peripheral neuropathy that manifests as extensive demyelinating of peripheral nerves and nerve roots. It is reported as the third most common PD-1-related neuromuscular disorder.78 According to the Japanese Adverse Drug Event Report database (JADER), patients with GBS/MFS (Miller-Fisher syndrome) account for 0.1% of all ICI-related NAEs.90 Another World Health Organization pharmacovigilance database VigiBase reported an incidence of 0.45% in combined ICI-related GBS during 2008 to 2018.91 However, the incidence of ICI-related GBS in patients with NSCLC has not been reported alone. Compared with MG, the onset time of ICI-related GBS is more variable, ranging from 4 weeks of ICI application to several months after completing the treatment cycle.92 The most remarkable symptoms of GBS are rapidly progressive limb weakness and loss/decrease of tendon reflexes, which peak within 28 days.93-96 Patients with ICI-related GBS in NSCLC usually suffer from sensory problems, containing paresthesia and numbness.95,96 The muscle weakness shows in symmetrical, arising from the lower limbs to upper arms, as well as bulbar muscles.97 Concomitant symptoms of muscular weakness are extensive loss or decrease of deep tendon reflexes, especially the most common tendon, biceps, and knee reflex, which are documented in 2 case reports with NSCLC.94-96 Cranial nerve deficits, particularly facial paralysis, ophthalmoplegia, and bulbar paralysis, can be observed.98 Patients with ICI-related GBS may also strike from the autonomic dysfunction, which influences multiple systems.99 To diagnose ICI-related GBS, auxiliary examinations are required. Brain and spinal MRI in 2 patients we collected showed pathological features, indicating a high sensitivity (Figure 2). Elevated protein levels combined with normal cell counts are a hallmark of GBS. It is reported that 64% of patients with GBS have an elevated protein level, and the cell count of 85% is normal.99 However, patients with new-onset symptoms have a relatively low incidence of elevated protein detection, increasing from 50% to approximately 90% after 2 weeks.99 Clinically, the best-known subtypes of GBS are AIDP and acute motor axonal neuropathy (AMAN), which distinguish from each other by the existence of sensory signs.100 The NCS is another necessary workup assisting the diagnosis of GBS. The NCS of patients of AIDP subtypes may reveal distal motor latency (DML), prolonged motor conduction velocity (MCV), conduction blocks, and abnormal temporal dispersion.100 The results of NCS of AMAN patients are more specific, with no demyelinating features with the decreased amplitude of distal CMAP.94 According to the treatment, IVIg and plasmapheresis are proved efficient, which applies to ICI-related GBS in patients with NSCLC according to the 2 case reports we collected.95,96 The IVIg is usually given for 5 days (0.4 g/kg/d).93 The normal regimen for plasma exchange is 5 sessions over 2 weeks, which is recommended to be applied within 4 weeks since the onset of GBS.93 Studies also indicate that the combination of plasmapheresis and IVIg does not have a significant difference compared with plasmapheresis alone.101 The efficacy of oral corticosteroids remains unclear, but the synergistic effects of combined use of IVIg and IV methylprednisolone cannot be excluded in patients.102 In a case report of pembrolizumab-related GBS with NSCLC, a combination of IV methylprednisolone and IVIg is proved to be effective.95 Prognosis of ICI-related GBS in patients with NSCLC is difficult to assess due to the individual variation. Most patients could get partial release within 2 to 4 weeks after the cease of disease progression. However, in some patients, diseases progress in a short period, resulting in death.94-96

Lambert-Eaton Myasthenic Syndrome
Lambert–Eaton myasthenic syndrome is a presynaptic disorder of neuromuscular junctions. It is reported that 50% to 60% of LEMS occurs with malignancies, which appears as a paraneoplastic syndrome.103 Lambert–Eaton myasthenic syndrome is induced by autoantibody against presynaptic P/Q-type VGCCs, which hampers over 95% of functional receptors responsible for signal transmission of neuromuscular junction.104 Due to the...
expression of mimic ectopic antigens in small cell lung cancer (SCLC), LEMS is commonly observed in patients suffering from it. However, ICI-related LEMS in patients with NSCLC is only documented as a case report, and its incidence has not been reported yet. Symptoms of ICI-related LEMS mainly appear as limb weakness, areflexia/hyporeflexia of deep tendons, and autonomic dysfunction. Imperceptible fatigue could be the incipient symptom, followed by weakness of proximal legs, which is regarded as the first symptoms by 80% of LEMS patients. Meanwhile, the weakness of arms may appear soon after the weakness of proximal legs, which suggests the principle of weakness spreading: from proximal, cranial parts to distal, caudal parts. Compared with MG, bulbar, axial, and ocular muscle weakness is mild or even absent. However, the incipient symptoms of nivolumab-related LEMS in a patient with NSCLC manifest as ptosis and photophobia. As for autonomic dysfunction, xerostomia is the most common one, which is always accompanied by a metallic taste. Constipation, dry eyes, and orthostatic hypotension may exist as well. Loss or decrease of deep tendon reflexes strengthens the suspicion of LEMS. In addition to clinical symptoms, to diagnose ICI-related LEMS in patients with NSCLC, antibody testing and electrophysiological studies need to be done for certain. P/Q type VGCC antibodies can be observed in nearly all patients with lung cancer accompanied by LEMS. However, in the serum of patients with LEMS, P/Q type VGCC could be negative. Similar symptoms could be induced by other blockers of a presynaptic receptor, suggesting that the seropositive P/Q type VGCC is not the only diagnostic criteria. The most prominent EMG characteristics of LEMS patients with NSCLC are called “post-exercise facilitation.” Initially, EMG shows a low amplitude of resting CMAP, which could be even lower after low-frequency (2-5 Hz) RNS. A rapidly progressive increase of CMAP after a high-frequency RNS (>10 Hz) or a maximal muscle contraction is then observed. Results of auxiliary examinations of the only 1 LEMS patient in NSCLC can be observed in the heat map (Figure 2). Symptomatic treatment and immunomodulatory therapy need to be applied to ICI-related LEMS patients with NSCLC. The strategy of symptomatic treatment is to increase the release of neurotransmitters. The most common agent is the 3,4-diaminopyridine (3,4-DAP), an inhibitor of presynaptic K⁺ currents. Blockade of presynaptic K⁺ channels prolongs the opening of VGCC, allowing the entry for more Ca²⁺ +, which therefore increases the release of intracellular Ca²⁺+ dependent-Ach. Acetylcholinesterase inhibitor pyridostigmine is less commonly used in combination with 3,4-DAP. If the application of 3,4-DAP could not achieve a preconceived effect, immunomodulatory therapy needs to be added. It is reported that combined application of azathioprine and prednisolone is more effective than prednisolone alone. Application of azathioprine needs to start from 15 mg/d to 30 mg/d, to maximal 80 mg/d to 100 mg/d, divided into 3 to 4 times a day. In the case report of nivolumab-related LEMS in a patient with NSCLC, pyridostigmine’s initial application only slightly relieves her wadding gait after the failure of oral prednisolone and another acetylcholinesterase inhibitor ambenonium, 3,4-DAP finally improves her manifestations. If the patient fails to respond to all these management, IVIg or plasma exchange is necessary, which shows relatively long-lasting improvements by reducing the concentration of circulating autoantibodies.

Other NAEs

In addition to the 4 relatively common ICI-related NAEs we mentioned, several rare ICI-related NAEs have not been mentioned in retrospective or prospective studies, and all of them are documented as case reports. Akathisia, necrotizing encephalitis, cerebral vasculitis, PRES, and neuromyelitis optica spectrum disorders (NMOSDs) induced by nivolumab manifested motor disturbance of cerebral dysfunction. Compulsive movements, nausea, vomiting, dyspnea, and urinary retention were also observed. In most instances, the application of steroids slightly or apparently improved the symptoms. Sedative drugs, antiepileptic treatments, IVIg, and plasmapheresis were applied based on the manifestations. One patient died with no apparent response to IVIg, antiepileptic treatments, and corticosteroids. Trousseau syndrome induced by pembrolizumab indicated right homonymous hemianopia. The MRI showed multiple cerebral infarcts because of brain metastasis. The patient died from hemorrhagic infarction soon after the second dose of pembrolizumab. Atezolizumab-induced cerebellar ataxia appeared with a progressive ataxic gait improved by long-term prednisolone application. Another patient treated with atezolizumab developed fatigue, diarrhea, anorexia, and pain in bilateral upper limbs leading the cessation of the application. She suddenly had visual loss a year later, which was diagnosed with optic neuritis. She recovered after the steroid pulse therapy and oral administration of prednisolone. Results of all these patients’ accessory examinations are recorded in the heat map, reflecting the positive and negative rate of each workup in different NAEs (Figure 2). Consensus guidelines have been published by the National Comprehensive Cancer Network (NCCN) Panel; therefore, we summarize a comprehensive diagnosis and treatment algorithm (Figure 3).

Notable Questions of Interest in Clinicians

Is the incidence of ICI-related NAEs higher in cancer patients with brain metastasis?

Immune checkpoint inhibitors have been proved effective in patients with various advanced malignancies. In previous clinical trials, cancer patients received ICI with untreated brain metastasis are mostly excluded from the penetration across blood-brain barrier (BBB), historically poor prognosis, and potential side effects to the nervous system. The incidence of ICI-related NAEs in patients with brain metastasis has not been documented as the lack of multicenter studies with large samples. However,
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#### Figure 3.

**Algorithm for the diagnosis and management of neurotoxicity.**

**Category**
- Peripheral neurological toxicity
- Central neurological toxicity

**Symptoms and sign**
- **Myasthenia gravis**
  - Progressive or fluctuating muscle weakness, generally proximal to distal, including cranial nerves with ptosis and possible respiratory muscle weakness. May have bulbar involvement (e.g., paresis, extracocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness).
- **Guillain-Barré syndrome**
  - Progressive symmetric muscle weakness with absent or decreased deep tendon reflexes. Examinations, facial, respiratory or ocular/bulbar muscle involvement. Autonomic nerve dysfunction.
- **Lambert-Eaton myasthenic syndrome**
  - Gradual and insidious proximal muscle weakness, autonomic features, and areflexia. Progress, photosensitivity.
- **Polyneuropathy**
  - Asymmetric or symmetric sensor-motor deficit. Sensory deficit may present as painful dysesthesia, hypop- or areflexia.
- **Encephalitis**
  - Confusion, headache, delirium, motor/hyponychy and/or speech abnormalities, altered behavior, seizures, short-term memory loss, decreased level of consciousness, focal weakness.
- **Alzheimers**
  - Extrapyramidal movement disorders, compulsive behavior, memory loss, depressed level of consciousness.
- **Meningitis**
  - Headache, photophobia, neck stiffness, may be febrile.
- **Transverse myelitis**
  - Acute or subacute weakness or bilateral motor or sensory changes, autonomic deficits, increased deep tendon reflexes.

**Suggested investigation**
- AchR antibodies and anti-muscule-skeletal tyro-kinase antibodies in blood. Pulpmetric function assessment, ESR, CRP, CK, aldolase, and anti-serial antibodies. ECOG, ESR, and TTE if respiratory insufficiency or elevated (CMR, EMG, NCS, or bronchoscopic evaluation.
- Brain MRI rule out spinal cord compression, myelitis, lumbar puncture (CSF), and elevations of anti-nuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA). ESR, MRI, lumbar puncture (CSF).
- Anti-IgG type VDS and SOX1 antibodies. Electrodiagnostic studies (ECS, include reduced CMAPs, amplitudes, 2 or decremental response at high R-wave.
- Brain MRI or CT, CBC, CMP.
- Brain MRI or CT, CBC, CMP, and/or lumbar puncture (CSF). WBC typically <5000, PCR for viral infection, electrolytes.

**Management recommendation**
- **General principles of neurotoxicity management**
- Asymptomatic or mild symptoms:
  - Intervention not indicated:
    - Continue immunotherapy per protocol.
- **Grade 2**
  - Moderate symptoms:
    - Limiting instrumental activities of daily living (ADL).
    - Delay immunotherapy per protocol.
    - Treat symptoms per local guidelines.
    - Consider 0.5 to 3.0 mg/kg/day methylprednisolone IV or PO equivalent.
- **Grade 3-4**
  - Severe symptoms, Limiting self-care ADLs, life-threatening:
    - Discontinue immunotherapy per protocol.
    - Obtain neurology consult.
    - Treat symptoms per local guidelines.
    - 1.0-2.0 mg/kg/day methylprednisolone IV or PO equivalent.
    - Add prophylactic antibiotics for opportunistic infections.

**For myasthenia gravis (added to general principles):**
- Pulmonary function testing.
- Anticholinesterases.
- Intravenous immunoglobulin (IV IgM) or IVIg.
- Intravenous immunoglobulin for Grade 3.
- Intravenous immunoglobulin for Grade 3-4.

**For Guillain-Barré syndrome (added to general principles):**
- Frequent neurologic evaluation and pulmonary function monitoring. Autonomic dysfunction or pulmonary function determine requirement for rapid transfer to ICU-level monitoring.
- Start IVIG or plasma exchange in addition to pulse dose methylprednisolone (Glcveperpart, prednisolone, or dexamethasone for pain).

**For Lambert-Eaton myasthenic syndrome (added to general principles):**
- LA-DECPAT, glucocorticoids, tacrolimus, calcineurin inhibitors.

**For polymyositis (added to general principles):**
- Glucocorticoids, prednisolone, or dexamethasone for pain.

**For encephalitis (added to general principles):**
- Consider IV acyclovir or IVIg ifOverview of the disease and its management.
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According to a small sample study with 23 patients (18 with prior local central nervous system [CNS] therapy) who suffer from melanoma with untreated brain metastasis (≤20 mm), the incidence of pembrolizumab-related ataxia and headache is 22% and 17%, respectively, which is higher in patients without brain metastasis we mentioned above.120 Meanwhile, in the same study, the incidence of headache in NSCLC patients with brain metastasis is 22%, and that of dizziness is 11%.121 Nevertheless, the increasing incidence of ICI-related NAEs in patients with brain metastasis compared with patients without intracranial malignancies could owe to the perilesional edema after the local surgery or small sample size. It is noteworthy that all the pembrolizumab-related NAEs in patients with brain metastasis of NSCLC are of grade 1 to 2, suggesting a relatively safe profile of ICI application in patients with brain metastasis.121 In this situation, we could only summarize the application of ICI in a patient with primary lesion and brain metastasis is relatively safe according to the rare occurrence of severe NAEs that are uncontrollable and lead to death.

**Does application of ICIs exacerbate preexisting autoimmune symptoms?**

In consideration of the treatment of patients with preexisting autoimmune disease, the application of ICI needs to be assessed meticulously. Both MG and LEMS could appear after the application of ICI, which may result from unmasking of dormant diseases or appearance of de novo diseases. It is reported that the application of PD-1/PD-L1 inhibitors exacerbates the symptoms of preexisting paraneoplastic syndrome in 50% (8/16) of patients suffered from cancer.106 A study based on SEER database identified patients with cutaneous melanoma combined with preexisting autoimmune disease received significant higher risk of irAEs in most organ systems.122 A meta-analysis of 6 reports discovered that preexisting autoimmune disease is a risk factor of irAE.123 All these data indicate that preexisting autoimmune disease augments the effect of ICI-related NAEs. Other autoimmune diseases, including myositis and myocarditis, are much higher in nivolumab-induced MG than idiopathic MG.124,125 Meanwhile, facial muscle weakness, bulbar symptoms, and panting also appear more frequently in nivolumab-related MG than idiopathic MG.125 Therefore, ICI also increases the possibility of acquiring other types of autoimmune diseases in cancer patients with preexisting autoimmune disease. According to the case reports we collected in NSCLC, there are no documentations of patients with preexisting autoimmune diseases who receive the ICI treatment. Studies focusing on the safety profile of ICI application to patients with preexisting autoimmune diseases need to be conducted in this condition.

**How to deal with patients with a relapse of NAEs?**

In patients treated with ICI, a notable phenomenon of relapse of ICI-related NAEs is observed. Studies indicate a higher incidence of it with the application of CTLA-4 inhibitors or a combined therapy than PD-1/PD-L1 monotherapy.40 This rate is also higher in patients who have ICI-related NAEs affected both the central and peripheral nervous system.40 It is noteworthy that patients with relapse of NAE are not treated with immunosuppressive therapy or only receive oral corticosteroids for a short period, which suggests an application of immunosuppressants to all patients with severe ICI-induced NAEs.40 We observe a relapse of PRES in a patient with NSCLC after a few weeks while the primary and relapsing treatments are not mentioned.24

**How is the prognosis of different descriptions of NAEs?**

The prognosis of different types of ICI-related NAEs remains unclear. Based on the case reports of ICI-related NAEs in patients with NSCLC, ICI-induced MG prognosis is relatively favorable, symptoms of 5 of 6 patients are improved by applying steroids pyridostigmine.18-20,22,23,25 The patient who died from MG receives similar treatment with others while achieving bad results due to the refusal of a mechanical ventilator, leading to hypercapnic respiratory failure.19 In a case report of ICI-related GBS, symptoms of the patient progress rapidly and show no obvious improvement to IVIg and plasma exchange, suggesting that an early diagnosis and treatment is necessary.15 In addition to the unresponsiveness to most therapeutic modalities, the patient died from necrotizing encephalopathy owes to the second application of ICI, which aggravates her previous symptoms. After the first application of nivolumab, symptoms have already appeared, which are considered partially attributed to hyponatremia and application of sertraline.14 In this condition, nivolumab is applied continuously, leading to the death of the patient.14 It has been reported that ICI-associated NAEs progress rapidly after the second application of ICI, although the symptoms after the first cycle are mild or can be relieved by excluding other risk factors.126 Clinicians need to carefully assess the severity of ICI-related NAEs and determine whether the stoppage or continuous ICI application is better for prognosis.

**Conclusions**

Immune checkpoint inhibitor–related NAEs are the disorder of central and peripheral nervous system, rare but may be fatal. A combination of PD-1/PD-L1 and CTLA-4 inhibitors increases the risk of ICI-induced NAEs compared with monotherapy. Time of occurrence ranges widely, but most concentrate within 1 to 5 weeks after the first dose initiation. Encephalitis, MG, GBS, and Lambert-Eaton are relatively common NAEs, which have been discussed in detail on clinical symptoms, diagnostic examinations, and treatment modalities. Steroids are main treatment modality to ICI-related NAEs. Intravenous immunoglobulin and plasmapheresis are necessary when manifestations deteriorate. To better understand the
diagnosis and treatment of ICI-related NAEs in NSCLC, further studies are needed.

Author Contributions
KC and YW collected data, reviewed the literature, analyzed all data, and wrote the manuscript. YZ collected data and wrote and revised the manuscript. RX collected data, rechecked the manuscript, and assisted in drawing. LT designed and revised the manuscript. All authors read and approved the final manuscript.

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