Review Article

Guillain-Barré Syndrome-Like Polyneuropathy Associated with Immune Checkpoint Inhibitors: A Systematic Review of 33 Cases

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Immune checkpoint inhibitors (ICIs) have been increasingly used in the treatment of various types of tumors with favorable results. But these treatments also led to a variety of immune-related adverse events (irAEs). Neurological irAEs such as Guillain-Barré Syndrome are rare and may have serious consequences once they occur. A systematic literature search was performed in PubMed and Embase for all case reports of GBS associated with ICIs published in English reporting on human beings from 1990 up to date. A total of 30 case reports (total patients = 33) were used for final analysis. The included cases were from 11 countries, covering 10 tumor types, with melanoma accounting for the largest number. The mean age was 62.2 ± 11.1 years old, and males were dominant (male: 26 and female: 7). The median time of initial symptoms was 8.2 weeks after the 1st dose of ICIs. The most common manifestations of GBS associated with ICIs were weakness, hyporeflexia or areflexia, and paresthesia in order. The GBS subtypes suggested by electrophysiological results were acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Miller Fisher syndrome (MFS). The protein level of CSF in patients with GBS related to ICIs was 180 ± 68 ± 152 ± 51 mg/dl.

Immediate termination of ICIs followed by intravenous immunoglobulin was the preferred treatment option. 72.7% of patients recovered or had residual mild dysfunction after treatment. Elderly male patients with melanoma were most likely to develop ICI-related GBS. The specific neurological symptoms, CSF analysis, and electrophysiological examination were important means of diagnosis.

1. Introduction

In the last decade, with a better understanding of the factors that promote or inhibit T cell response, great progress has been made on tumor immunotherapy. Immune checkpoint inhibitors (ICIs) have become a powerful clinical strategy for treating cancer, including an antibody targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4, e.g., ipilimumab), antibodies directed against programmed cell death protein-1 (PD-1, e.g., nivolumab, pembrolizumab, and cemiplimab), and anti-PD-1 ligand (PD-L1, e.g., atezolizumab, durvalumab, and avelumab) [1]. These drugs can be used alone or in combination with other immunotherapy [2] or chemotherapy [3] to improve the survival of cancer patients. Currently, it has been used for the treatment of tumors of lung, kidney, liver, bladder and breast cancer, melanoma, and lymphomas [4–6]. ICIs improve the prognosis and quality of life of patients, whereas the increase of use also brings various immune-related adverse events (irAEs). The dermatologic, gastrointestinal, pulmonary, hepatic, and endocrine systems were most frequently involved.

Cases of neurological irAEs are rare, accounting for less than 3% [7]. So far, the best-characterized central nervous system irAEs are encephalitis and meningitis. And neurologic irAEs known to be most relevant to the peripheral nervous system are peripheral neuropathies, GBS, myasthenia gravis, and myositis [8]. Once they occur, such as encephalitis, Guillain-Barré syndrome, or myasthenia gravis, they can develop into serious consequences or even death.

Epidemiology shows that nearly two-thirds of patients with GBS have a recent history of infection before the illness [9]. GBS with potentially life-threatening consequences occurs in approximately 0.1-0.2% of patients treated with ICIs [10]. To date, information on the incidence,
characteristics, and outcomes of GBS associated to ICIs treatment is very limited. And the available information varies widely in diagnosis and treatment. Multidisciplinary treatment of tumors urgently requires neurologists and oncologists to accurately understand the clinical manifestations and treatment of ICI-related GBS.

This review summarized the published data on GBS or GBS-like disease occurring in patients after treatment with ICIs from 1990 up to date and analyzed their time patterns of occurrence, clinical presentation, diagnosis, treatment, and prognosis.

2. Methods

A systematic literature search was performed in PubMed and Embase for all case reports of GBS associated with ICIs published in English reporting on human beings from 1990 up to date. For the case reports search, the keywords used were as follows: ["Guillain-Barré Syndrome" OR "acute inflammatory demyelinating polyradiculoneuropathy" OR "Miller Fisher Syndrome" OR "acute motor axonal neuropathy" OR "acute motor-sensory axonal neuropathy"] AND ["Immune Checkpoint Inhibitors" OR "Immune Checkpoint Blockers" OR "PD-L1 Inhibitors" OR "Programmed Death-Ligand 1 Inhibitors" OR "CTLA-4 Inhibitors" OR "Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitors" OR "PD-1 Inhibitors" OR "Programmed Cell Death Protein 1 Inhibitor"].

Abstracts of medical conference were excluded. For each case, we extracted data on demographics and clinical manifestations and adjuvant examinations (imaging, cerebrospinal fluid, and electrophysiology). If gender, age, GBS clinical variation [11], electrophysiological subtype [12], or results of the relevant examination were not explicitly reported in the article, this case could not be considered for analysis. The search was conducted by Yan Li and Xiuchun Zhang. The selection of the articles should be agreed upon by the above two persons.

GraphPad Prism 8 was used for statistical analysis, and continuous data were expressed in the form of mean ± standard deviation or median. P < 0.05 was considered statistically significant. Since the proportion of males and females in the included cases was significantly different, unpaired t-test was used to analyze the ages of males and females.

Because the patient’s personal information was provided in the original case report, authorization from the Ethics Committee was not required for this study.

3. Results

Using the search terminology, 38 case reports were identified from our database search, covering the period from January 2008 to February 2021. Three patients were excluded due to lack of age and CSF protein concentration, respectively. One case report was excluded because it was written in Japanese. Two case reports were not included because the diagnosis of GBS was ambiguous due to a disease progression similar to acute-onset CIDP. In addition, two patients with a history of GBS had no serious toxicities or deterioration of the previous autoimmune disorders after ICI therapy.

The two patients were also excluded. A total of 30 case reports (total patients = 33) were used for final analysis [13–42]. According to the diagnostic criteria of GBS in NINDS, all the above 33 cases were consistent with the features of GBS. The clinical data and diagnostic details of all included patients were summarized in Tables 1–3.

3.1. Demographic Characteristics. GBS cases (n = 33) were from the United State (n = 13), United Kingdom (n = 3), Japan (n = 2), Italy (n = 2), Belgium (n = 2), Australia (n = 2), China (n = 1), Greece (n = 1), Netherlands (n = 4), France (n = 2), and Germany (n = 1) (Table 1). Of the 33 cases, twenty-six of these cases were male and seven were female, with an average of 62.2 ± 11.1 years (median: 65 years and range: 37-81 years). There was a male preponderance in 33 ICI-associated GBS patients we collected, with 3.7 times as many cases as female (26 vs. 7 cases: 78.8% vs. 21.2%). There was a significant difference between male and female ages at onset (mean: 64.4 ± 10.3 vs. 54.1 ± 11.1 years, P = 0.0278). The reports of comorbidities were variable, and no epidemics of specific diseases had been observed, so we did not analyze the comorbidities.

3.2. Immune Checkpoint Inhibitors and Tumor Type. Of ICI-associated GBS patients, sixteen patients exposed to nivolumab, eleven patients were investigated with ipilimumab, and seven patients were treated with pembrolizumab. Of these, four patients received nivolumab in combination with ipilimumab, and one patient received nivolumab in combination with pembrolizumab. In the above cases, the types of tumor the patients suffered from were melanoma (n = 20) [13, 14, 16, 17, 23, 24, 28, 29, 31–37, 39–42], lung tumor (n = 7) [18, 21, 25, 26, 28, 30, 38], urinary tumor (n = 5) [13, 15, 19, 20, 22], and nasal cancer (n = 1) [27]. The details were summarized in Tables 4 and 5.

3.3. Clinical Features of GBS Spectrum. The onset time of symptoms in 32 patients was analyzed, and the results suggested that the median time was 8.2 weeks after the initiation of ICI treatments. The minimum was 0.7 weeks (5 days) [37], and the maximum was 59 weeks [19]. As shown in Table 1, the time to neurological plateau was mentioned in 23 cases, with an average of 16.0 ± 8.4 days (range 7–44 days). The most common manifestations of GBS associated with ICIs were weakness (93.9%, 31/33), hyporeflexia or areflexia (90.9%, 30/33), and paresthesia (81.8%, 27/33). Among them, sensory symptoms and paraparesis or tetraparesis cooccurred in 45.5% (15/33) of cases. Other less common symptoms included cranial nerve involvement (20.7%, 7/33), dysphagia or dysarthria (18.2%, 6/33), respiratory symptoms (21.2%, 6/33), and ataxia (9.1%, 3/33). There were also 2 rare cases of GBS patients with dysautonomia as the onset symptoms [17, 36]. The Hughes Functional Grading Scale (HFGS) [43] was used to evaluate the clinical severity, and higher numbers indicated more severe disability. The average was 3.85 ± 1.42, with a high score of 6 and a low score of 1 (Table 2).

3.4. Electrophysiological, CSF, and Imaging Results. Twenty-seven patients underwent electrophysiological examination, and 18 cases had detailed electrophysiological reports. In
| Case | Article | Country | Age | Sex | Tumor type | ICIs | Time of GBS onset after the initiation treatment (week) | Time to neurological plateau (days) | GBS diagnosis |
|------|---------|---------|-----|-----|------------|------|------------------------------------------------------|-----------------------------------|----------------|
| 1 | Muralikrishnan, S et al. [14] | USA | 65 | Female | Melanoma | Pembrolizumab | 4 weeks | 44 | Clinical+CSF+electrophysiology |
| 2 | Han, C et al. [15] | China | 55 | Male | RCC | Pembrolizumab | 16 weeks | No mention | Clinical+CSF+electrophysiology |
| 3 | Arora, A et al. [16] | USA | 70 | Male | Melanoma and prostate cancer | Pembrolizumab | 12 weeks | 16 | Clinical+CSF+electrophysiology |
| 4 | Yuen, C et al. [17] | USA | 66 | Male | Melanoma | Nivolumab | 12 days (1.7 weeks) | 34 | Clinical+CSF+electrophysiology |
| 5 | Pomerantz, M et al. [18] | Italy | 58 | Male | SCLC | A combination of nivolumab and pembrolizumab | 59 days (8.4 weeks) | No mention | Clinical+CSF+electrophysiology |
| 6 | Pierrard, J et al. [19] | Belgium | 70 | Male | Urothelial carcinoma | Nivolumab | 59 weeks | 14 | Clinical+CSF+electrophysiology |
| 7 | McNeill, C. J et al. [20] | UK | 68 | Male | RCC | Nivolumab | 8 weeks | 13 | Clinical+CSF+electrophysiology |
| 8 | Kyriazoglou, A. et al. [22] | Greece | 74 | Male | Bladder cancer | Nivolumab | 8 weeks | 15 | Clinical+CSF+electrophysiology |
| 9 | Mazzaschi, G et al. [21] | Italy | 80 | Male | Lung adenocarcinoma | Nivolumab | 12 days (1.7 weeks) | 22 | Clinical+CSF+electrophysiology |
| 10 | Gravbrot, N et al. [23] | USA | 71 | Male | Melanoma | Ipilimumab | 10 weeks | Several days | Clinical+CSF+electrophysiology |
| 11 | Wilson, R et al. [24] | UK | 52 | Male | Melanoma | Nivolumab | 4 weeks | 7 | Clinical+CSF+electrophysiology |
| 12 | Thapa, B et al. [25] | USA | 60 | Male | Lung adenocarcinoma | Nivolumab | 14 weeks | No mention | Clinical+CSF+electrophysiology |
| 13 | Ong, S et al. [26] | UK | 66 | Male | Lung adenocarcinoma | Pembrolizumab | 6.5 weeks | 16 | Clinical+electrophysiology |
| 14 | Nukui, T et al. [27] | Japan | 45 | Male | Nasal cancer | Nivolumab | 10 weeks | 14 | Clinical+CSF+electrophysiology |
| 15 | Manam, R et al. [28] | USA | 73 | Male | Lung adenocarcinoma | Pembrolizumab | 3 weeks | No mention | Clinical+CSF+electrophysiology |
| 16 | Manam, R et al. [28] | USA | 81 | Male | Melanoma | Pembrolizumab | 10 weeks | No mention | Clinical+CSF+electrophysiology |
| 17 | Garcia, C. A et al. [29] | USA | 55 | Male | Melanoma | Ipilimumab | 6 weeks | No mention | Clinical+CSF+electrophysiology |
| 18 | Fukumoto, Y et al. [30] | Japan | 66 | Male | NSCLC | Nivolumab | 3 weeks | 16 | Clinical+CSF+electrophysiology |
| 19 | Cafuir, L et al. [31] | USA | 42 | Male | Melanoma | Ipilimumab | 10 weeks | 13 | Clinical+CSF+electrophysiology |
| 20 | Baird-Gunning, J. J. D et al. [31] | Australia | 58 | Female | Melanoma | Nivolumab | 10 days (1.4 weeks) | 12 | Clinical+CSF+electrophysiology |
| Case | Article | Country   | Age | Sex | Tumor type                          | ICIs                       | Time of GBS onset after the initiation treatment (week) | Time to neurological plateau (days) | GBS diagnosis                          |
|------|---------|-----------|-----|-----|-------------------------------------|---------------------------|--------------------------------------------------------|--------------------------------------|----------------------------------------|
| 21   | Supakornnumporn, S et al. [33] | USA       | 77  | Male | Melanoma                           | Nivolumab, Ipilimumab     | 10 weeks                                              | 14                                   | Clinical+CSF electrophysiology         |
| 22   | Schneiderbauer, R et al. [34]  | German    | 51  | Male | Melanoma                           | Nivolumab                 | 20 weeks                                              | No mention                           | Clinical+CSF electrophysiology         |
| 23   | Patel, R. J et al. [35]        | USA       | 71  | Male | Melanoma and papillary thyroid cancer | Ipilimumab                | 10 weeks                                              | 10                                   | Clinical+electrophysiology            |
| 24   | Kelly Wu, W et al. [36]        | USA       | 37  | Female | Melanoma and papillary thyroid cancer | Ipilimumab                | No mention                                            | 9                                    | Clinical+CSF electrophysiology         |
| 25   | Gu, Y et al. [37]              | Australia | 49  | Female | Melanoma                           | Ipilimumab, Nivolumab     | 5 days (0.7 weeks)                                    | 11                                   | Clinical+CSF electrophysiology         |
| 26   | Jacob, A et al. [38]           | USA       | 68  | Female | Papillary thyroid cancer           | Ipilimumab                | 12 weeks                                              | 14                                   | Clinical+CSF electrophysiology         |
| 27   | Gaudy-Marqueste, C et al. [40] | France    | 65  | Male | Melanoma                           | Ipilimumab                | 6 weeks                                               | 11                                   | Clinical+CSF                          |
| 28   | Bot, I et al. [41]             | Netherlands | 63  | Male | Melanoma                           | Ipilimumab                | 12 weeks                                              | A few days                           | Clinical+CSF electrophysiology         |
| 29   | Wilgenhof, S et al. [42]       | Belgium   | 57  | Female | Papillary thyroid cancer           | Ipilimumab                | 8 weeks                                               | No mention                           | Clinical+CSF electrophysiology         |
| 30   | de Maleissye, M.F. et al. [39] | France    | 45  | Female | Melanoma                           | Pembrolizumab             | 9 weeks                                               | 21                                   | Clinical+CSF electrophysiology         |
| 31   | Janssen, J.B.E. et al. [42]    | Netherlands | 74  | Male | Prostate cancer                    | Pembrolizumab             | 6 weeks                                               | 21                                   | Clinical+CSF electrophysiology         |
| 32   | Janssen, J.B.E. et al. [13]    | Netherlands | 67  | Male | Melanoma                           | Nivolumab                 | 3 weeks                                               | 7                                    | Clinical+CSF                          |
| 33   | Janssen, J.B.E. et al. [13]    | Netherlands | 55  | Male | Melanoma                           | Pembrolizumab             | 16 weeks                                              | 15                                   | Clinical+CSF                          |

LEs: lower extremities; UEs: upper extremities; NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer; RCC: renal cell carcinoma. Time to Nadir: days between the onset of neurological symptoms and the development of the worst clinical symptoms (no progression).
Table 2: The clinical data and diagnostic details of all included patients.

| Case | Onset | Motor | Sensory | Reflex | Autonomic disturbances | Respiratory involvement | Hughes scale |
|------|-------|-------|---------|--------|------------------------|-------------------------|--------------|
| 1    | LEs ascending numbness bilaterally | Muscle weakness in lower limbs and left hand | Left tongue numbness and diminished facial sensation. | Generalized areflexia | None | No | 2 |
| 2    | Weakness and numbness of the extremities | A mild decrease in muscle strength of the limbs | Paresthesia of the four extremities | Absence of tendon reflex of the limbs. No pathological reflex. | None | No | 1 |
| 3    | Progressive bilateral LE weakness | Decreased strength in lower extremities | Slight impairment of touch and pinprick sensation, worsening back pain and painful burning in feet bilaterally | Bilaterally absent patellar and ankle reflexes | None | No | 6 |
| 4    | Bilateral finger and toe paresthesia followed by weakness of the lower and then upper limbs | Absent pinprick sensation and vibratory sensation | Generalized areflexia | Tachycardia, hypotension, Respiratory distress | None | No | 6 |
| 5    | Bilateral LE paresthesias, pain | Bilateral LE weakness and progressively worsened to a complete inability to ambulate | Diminished sensory perception in LEs, pinprick over all distal extremities, marked decrease in vibration sensation and absent proprioception in LEs | Generalized areflexia | None | No | 4 |
| 6    | Rapidly progressing weakness of LEs | Rapidly progressing upper limb weakness over 2 weeks | General weakness, slurred speech, double vision, difficulty swallowing, within 72 hours, rapidly worsening bulbar symptoms | Normal tone, power and deep tendon reflexes | None | No | 3 |
| 7    | Progressive weakness and sensory disturbance in face and limbs | Paresthesia of his hands and feet, an unsteady gait | Areflexia of the 4 limbs and absent pathologic reflexes | None | Shortness of breath | 5 |
| 8    | Muscle weakness and fatigue | Severe proximodistal weakness in the UEs and LEs | Impairment of position sense, vibration, stereognosis, and graphesthes | Areflexia of the 4 limbs and absent pathologic reflexes | None | No | 3 |
| 9    | Paresthesia and burning pain arose in LEs, followed by a progressive bilateral weakness | Symmetric distal dominant weakness and dramatically worsened. Loss of fine motor control on distal UEs | Pain and severe numbness. | Hypoareflexia and decreased deep tendon reflexes | None | No | 4 |
| 10   | Severe, progressive, symmetric ascending weakness | The paralysis progressed to inability to stand and arm weakness Mild dysphagia | Without sensory loss | Unobtainable deep tendon reflexes | None | Shortness of breath | 4 |
| 11   | Headache and generalized tiredness | Bilateral facial weakness, distal limb weakness | Progressive hand and feet numbness | Reduced deep tendon reflexes | None | No | 3 |
| 12   | Severe weakness of all extremities | Mild to moderate decrease in motor strength in all 4 extremities, LEs worse than UEs | Sensory loss of vibration/properitoception in bilateral LEs | Diminished reflexes in bilateral LEs but normal reflexes in bilateral UEs | None | No | 4 |
| Case | Onset | Motor | Sensory | Reflex | Autonomic disturbances | Respiratory involvement | Hughes scale |
|------|-------|-------|---------|--------|------------------------|-------------------------|--------------|
| 13   | LE pain, paresthesia and weakness | UE weakness and a lower motor neuron pattern of right-sided facial weakness, Bilateral, predominantly distal LE weakness, Bed-bound | Reduced sensation | Generalized areflexia | None | No | 2 |
| 14   | Diplopia, muscle weakness, and numbness of extremities | Right external ophthalmoplegia, left facial nerve palsy and bulbar palsy, severe muscle weakness | Bilateral facial dysesthesia | Absent deep-tendon reflexes | None | No | 4 |
| 15   | Generalized weakness | Progressive weakness in the bilateral LEs greater than the UEs | Without sensory loss | Absent deep tendon reflexes in the bilateral UEs and LEs | None | No | 3 |
| 16   | Progressive weakness in the bilateral LEs and then spreading to the bilateral UEs | A strength of 2/5 in the bilateral UEs and 0/5 in the bilateral LEs and no bulbar muscle weakness | Without sensory loss | Areflexia | None | Requiring mechanical ventilation | 4 |
| 17   | Paresthesias in distal LEs bilaterally | Ascending weakness | Ascending paresthesias | Loss of deep tendon reflexes | None | No | 2 |
| 18   | Muscle weakness of the LEs | Weakness rapidly progressed and became bed-bound | Paresthesias of the distal limbs | Absence of deep tendon reflexes of the four extremities | None | No | 4 |
| 19   | Bilateral thigh weakness and paresthesia of the soles of his feet | LEs weakness, worsened rapidly | Pain and numbness, vibration in the toes impaired | Tendon reflexes in the LEs were absent. | None | No | 3 |
| 20   | Bilateral ptosis and external ophthalmoplegia | Proximal upper and lower limb weakness, neck flexion weakness | Marked truncal and limb ataxia were evident accompanied by impaired proprioception. | Areflexia | None | No | 2 |
| 21   | Rapidly progressive numbness and tingling sensation in both hands and feet, generalized muscle weakness with multiple falls | Severe distal and proximal muscle weakness in both upper and lower extremities | Loss of all sensory modalities in distal upper and lower extremities | Generalized areflexia | None | No | 4 |
| 22   | Muscular weakness in both legs and peripheral paresthesias | Muscular weakness in both legs and peripheral paresthesias | Formication in both hands, bilateral hypoesthesia of the legs up to the upper thigh | Absent tendon reflexes in both legs | None | No | 1 |
| 23   | Progressive LE weakness | Progressive and ascending muscle weakness | Without sensory loss | Absent deep tendon reflexes | None | No | 4 |
| 24   | Tonically dilated pupil, gastrointestinal dysmotility, urinary retention, and profound orthostatic hypotension | Worsening dysarthria, generalized weakness | Ascending paresthesias, absent proprioception | Absent deep tendon reflexes | None | No | 5 |
| Case | Onset | Motor | Sensory | Reflex | Autonomic disturbances | Respiratory involvement | Hughes scale |
|------|-------|-------|---------|--------|------------------------|------------------------|--------------|
| 25   | Painful paresthesia in the extremities | Proximal loss of antigravity power and loss of independent mobility | Sensory loss | Absent reflexes | Nausea, postural hypotension constipation | No | 4 |
| 26   | Fatigue and bilateral LE weakness | Profound weakness in lower extremities, progressive loss of motor function | Tingling sensation in feet, progressive loss of sensory function | Loss of deep tendon reflexes in all extremities associated with complete lack of strength | None | Respiratory muscle paralysis | 5 |
| 27   | Pruritus, abdominal meteorism, and nausea | Symmetrical weakness in the 4 limbs | Mild bilateral hypoesthesia in the extremities | Disappearance of deep tendon reflexes | Abdominal meteorism and nausea | Worsening of the respiratory function | 6 |
| 28   | Paresthesias of the feet and fingertips and unsteady gait | A mild tetraparesis | Sensory loss in both hands and feet | Generalized areflexia | None | No | 5 |
| 29   | Dysesthesia (numbness and tingling) at the hands and feet | Rapidly ascending loss of motor function | Rapidly ascending loss of sensory function | Loss of the deep tendon reflexes | None | Respiratory insufficiency | 5 |
| 30   | Paresthesia and hypoesthesia of all limbs | Rapidly followed by symmetrical motor weakness in legs Peripheral facial paralysis | Paresthesia and hypoesthesia | Areflexia in the legs | None | No | 6 |
| 31   | Painful fingers and loss of taste | Weakness in all extremities | Sensory loss in all extremities | Areflexia in both legs | None | Respiratory function was affected | 6 |
| 32   | Muscular pains in his arms and legs without paralysis | Loss of motor functions in the hands and LEs | Loss of sensor functions in the hands and LEs | Areflexia of LEs | None | Respiratory function preserved | 4 |
| 33   | Ascending weakness, paresthesia, and sensory loss progressive | Weakness of the legs | Sensory disturbances of the lower extremities | Areflexia | None | Respiratory function preserved | 3 |

LEs: lower extremities, UEs: upper extremities.
| Case | NCS finding | Protein (15-45 mg/dl) | Cell (<5/μl) | Imaging | Treatment | Outcome |
|------|-------------|----------------------|--------------|---------|-----------|---------|
| 1    | 4 weeks after ICIs: not suggestive of neuropathy | 78 OL (+) | 17 | None | IVIG over 5 days for the first time | Significant improvement in muscle weakness. 18 days after discharge, the disease developed an ascending paralysis of the extremities. |
| 2    | 44 days later: acute and chronic demyelinating polyneuropathy | 175 OL (-) | 3 | MRI of the brain and spinal cord was normal. | PLEX for 7 days and solumedrol for 5 days instead of IVIG for reoccurrence | Melanoma progression occurred about 1 year after the last dose of pembrolizumab. Rechallenging with ipilimumab. Only ongoing bilateral leg tingling and diarrhea |
| 3    | Acute motor and sensory axonal neuropathy | 58.33 | 8 | Spinal MRI: abnormal thickening and enhanced posterior nerve roots (L4-L5, L5-S1), no features of metastatic disease | Dexamethasone for 6 days and IVIG for 5 days | No recurrence of tumor |
| 4    | AIDP | 405 | 4 | MRI of the brain as well as the lumbar and thoracic spine MRI: no clear cord or cauda equina involvement despite spine metastases | IVIG+prednisone+PLEX Life-sustaining therapies | Hydrocephalus, ventricular enlargement and bed-bound |
| 5    | AIDP | 124 | 41 | Spinal MRI: severe stenosis of lumbar spinal canal | IVIG for 5 days | No other potential agents were given and alive 6 months after the use of last immunotherapies. |
| 6    | AIDP | 105 | 8 | Brain as well as the lumbar and thoracic spine MRI: no clear cord or cauda equina involvement despite spine metastases | IVIG for 5 days and methylprednisolone during 7 days | A rapid clinical improvement was observed within the first 3 days. Methylprednisone was tapered progressively over 10 weeks. Completely recovered. 6 months later, cancer remains stable. |
| 7    | MFS | 175 | 5 | Brain and cervical spine MRI: normal | IVIG and intravenous methylprednisolone followed by oral prednisolone | Respiratory function and motor weakness improved after 9 days of corticosteroid treatment. Rehabilitation after 3 months of treatment Improvement. |
| 8    | AIDP | 140 | 2 | Spinal MRI: abnormal thickening and enhanced posterior nerve roots (L4-L5, L5-S1), no features of metastatic disease | IVIG for 5 days along with prednisone for 1 month | Disease progressed with increased number and size of lung metastases. Died from sepsis |
| Case | NCS finding | Protein (15-45 mg/dl) | Cell (<5/μl) | Imaging | Treatment | Outcome |
|------|-------------|----------------------|-------------|---------|-----------|---------|
| 9    | AIDP        | 88                   | 2           | Brain and spinal MRI: no evidence of metastases or ischaemic and/or hemorrhagic lesions | Methylprednisolone IVIG for 5 days | Without clinical benefit |
|      |             |                      |             |         | Prednisone | Leg weakness, numbness in patient’s fingers, and paresthesia dramatically improved. |
|      |             |                      |             |         | IVIG       | A further improvement was obtained after 2 weeks of prednisolone. |
| 10   | Acute sensorimotor polyradiculoneuropathy with mixed axonal/demyelinating | <45 <5 | Spinal CT: normal | IVIG for 5 days and prednisone 30 mg daily at the same time | 3 weeks later, improved rapidly and transition to pembrolizumab with no evidence of GBS |
|      |             |                      |             |         | Prednisone IVIG | Good recovery |
| 11   | AIDP        | 230                  | 0           | Spinal MRI: normal | IVIG | Symptoms continued to worsen. |
|      |             |                      |             |         | Prednisone IVIG | Minimally improved but prevented further progression |
| 12   | AMAN        | 37 mg/dl but elevated IgG levels | 2 | Spinal MRI: degenerative changes with no evidence of cord compression | Methylprednisolone and IVIG | 19 days after admission, weakness and numbness mostly resolved. |
|      |             |                      |             |         | Prednisone | 1 month later, neurological recovery except for mild residual paresthesias of the feet |
| 13   | AIDP        | No lumbar puncture was performed. | | Spinal MRI: degenerative changes with no evidence of cord compression | Methylprednisolone and IVIG | Multiple cranial neuropathies were moderately improved after 4 weeks of treatment. |
|      |             |                      |             |         | Prednisone | Muscle weakness remarkably improved after the 3 courses of therapy. |
|      |             |                      |             |         | IVIG | Strength diminished to 2/5 in the bilateral UEs and LEs. |
| 14   | Multiple cranial neuropathy and AIDP | 350 7 | Lumbar spine MRI: a reduction of gadolinium enhancement of nerve roots and cauda equina | IVIG | Respiratory status worsened. |
|      |             |                      |             |         | Steroid pulse therapy | Respiratory status improved, and motor function gradually recovered. |
|      |             |                      |             |         | Methylprednisolone along with IVIG PLEX | Acute hypoxic respiratory failure, requiring mechanical ventilation. After five days of treatment without any clinical improvement. |
| 15   | AIDP        | 680                  | <5          | Brain CT: a hemorrhage within one of his metastatic lesions and associated vasogenic edema | Methylprednisolone along with IVIG for 5 days | A hemorrhage within one of metastatic lesions and associated vasogenic edema. |
| 16   | AIDP        | 560                  | <5          | Brain CT: a hemorrhage within one of his metastatic lesions and associated vasogenic edema | Methylprednisolone along with IVIG for 5 days | Died after the withdrawn of care |
| Case | NCS finding | Protein (15-45 mg/dl) | Cell (<5/µl) | Imaging | Treatment | Outcome |
|------|-------------|-----------------------|--------------|---------|-----------|---------|
| 17   | AIDP        | 175                   | Lymphocytic pleocytosis | Brain and spinal MRI: abnormal enhancement involving the bilateral 5th, 7th and 8th cranial nerves, cauda equina nerve roots as well as the conus surface and peripheral nerves at the thoracolumbar junction | Methylprednisolone | Motor symptoms in hands and lower extremities improved rapidly after 2 days and gradually recovered over a 12-week period. Weakness resolved completely, residual minimal paresthesias. Symptoms worsened gradually improved. 3 months later, he was able to walk with a cane. |
| 18   | AIDP        | 339                   | 4            | Spinal MRI: diffuse enhancement surrounding the entire conus and all of the nerve roots | Prednisone (60 mg/day) IVIG (0.4 g/kg) for 5 days | Partial response systemically and neurologic improvement 6.5 months later, melanoma progressed. |
| 19   | Asymmetric, subacute to early chronic and ongoing lumbar polyradiculoneuropathy with axonal involvement and demyelinating | >300                | 1            | Spinal MRI: diffuse enhancement surrounding the entire conus and all of the nerve roots | Dexamethasone | Modest clinical improvement Significant functional improvement and complete recovered at last. But melanoma had progressed. Dysphagia requiring nasogastric tube for feeding |
| 20   | MFS and demyelinating sensorimotor polyneuropathy | 125                  | 0            | Thoracic spine and lumbar spine CT: degenerative changes | IVIG 2 g/kg for 5 days and methylprednisolone followed by a weaning dose of oral prednisolone | Modest clinical improvement Significant functional improvement and complete recovered at last. But melanoma had progressed. Dysphagia requiring nasogastric tube for feeding |
| 21   | AIDP        | 86                    | 0            | Thoracic spine and lumbar spine CT: degenerative changes | IVIG over 5 days Prednisone 90 mg/day | After 6 months, neurological condition improved significantly and the dysphagia completely was resolved. Numbness was still present but improved. |
| 22   | AIDP        | 73                    | <5           | Thoracic spine and lumbar spine CT: degenerative changes | IVIG for 5 days Methylprednisolone | Did not lead to any clinical improvement Clinical recovery started 48h later and was nearly complete after 6 weeks. |
| 23   | Acute sensorimotor polyradiculopathy with mixed axonal/demyelinating features | 39                    | <5           | Thoracic spine and lumbar spine CT: degenerative changes | IVIG | Marked improvement on treatment day 5 |
| 24   | GBS presenting as dysautonomia, a length-dependent, sensorimotor polyneuropathy with axonal and demyelinating properties | No lumbar puncture was performed. | | | IVIG | Dysautonomia and weakness persisted, and cardiovascular and respiratory status improved by 2 months. Persistent urinary retention, oropharyngeal dysphagia, and generalized weakness |
### Table 3: Continued.

| Case | NCS finding                     | Protein (15-45 mg/dl) | CSF Cell (<5/μl) | Imaging                  | Treatment                                                                 | Outcome                                                                 |
|------|---------------------------------|-----------------------|-------------------|--------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 25   | AMSAN with autonomic symptoms   | 115                   | 15                | Spinal MRI: normal       | IVIG (0.4 g/kg/d) for 5 days Methylprednisolone (1 g/d for 5 days, then 500 mg/d for 3 days) followed by tapering oral prednisolone (1 mg/kg/d) PLEX (5 changes over 2 weeks, followed by weekly exchanges) | Symptoms stabilized with mild improvement, yet one month later, it developed worsening weakness and ongoing painful paresthesia. Persistent nausea coupled with postural hypotension and constipation. 6 weeks later (12 weeks after initial treatment), the patient had only mild weakness. 9 months later, melanoma progressed. Within 2 hours, respiratory muscle paralyzed, and ventilator support was applied. She was extubated after 11 days and expired within a few hours. |
| 26   | GBS                             | 85                    | 0                 | Spine MRI: normal        | IVIG+PLEX                                                                 | Clinical status did not improve. Died of multivisceral failure within a few days |
| 27   | Acute, generalized, symmetrical, and sensorimotor neuropathy, impossible to distinguish axonal or demyelinating disorder because of severe limb edema | 160                   | 0                 | Methylprednisolone PLEX | The muscle strength of all limbs slightly increased. But 3 days later, died from respiratory insufficiency Recovery | The neurologic symptoms reached the peak within 3 weeks and decreased over the next 2 months. A slight improvement with these treatments 2 months later, died from pneumonia The pain was greatly diminished. 8 months later, the motor and sensor function of extremities were still slowly recovering. |
| 28   | AMSAN                           | 89                    | 0                 | Cervical spine MRI: normal | IVIG                                                                 | The mild persistent weakness of his feet extensors and mild sensory loss and ataxia |
| 29   | AIDP                            | 167                   | <2                | Brain and spinal MRI: normal | Methylprednisolone IVIG | AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher syndrome; IVIG: intravenous immunoglobulin; PLEX: plasma exchange; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; OL: oligoclonal bands. | |
| 30   | AIDP                            | 56                    | Normal            |                          | Methylprednisolone IVIG                                              | The mild persistent weakness of his feet extensors and mild sensory loss and ataxia |
| 31   | MFS                             | 81 OL (+)             | Normal            | Central nervous system imaging showed no cerebral or vertebral pathology. | Prednisolone IVIG PLEX                                              | AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher syndrome; IVIG: intravenous immunoglobulin; PLEX: plasma exchange; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; OL: oligoclonal bands. |
| 32   | GBS                             | 107.5                 | 61                |                          | Prednisolone IVIG                                                  | AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher syndrome; IVIG: intravenous immunoglobulin; PLEX: plasma exchange; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; OL: oligoclonal bands. |
| 33   | GBS                             | 204.6 OL (+)          | Normal            |                          | Prednisolone IVIG Methylprednisolone                                  | AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher syndrome; IVIG: intravenous immunoglobulin; PLEX: plasma exchange; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; OL: oligoclonal bands. |
Table 4: Tumor type and immune checkpoint inhibitors.

| Tumor type      | Pembrolizumab | Nivolumab | Ipilimumab | Nivolumab and ipilimumab | Pembrolizumab and nivolumab |
|-----------------|---------------|-----------|------------|---------------------------|-----------------------------|
| Melanoma (20)   | 6             | 3         | 7          | 4                         |                             |
| (M : F = 14 : 6)|               |           |            |                           |                             |
| Lung cancer (7) |               |           |            |                           | 1                           |
| (M : F = 6 : 1) |               |           |            |                           |                             |
| URF (1)         |               |           |            |                           |                             |
| NSCLS (1)       |               |           |            |                           | 1                           |
| SCLS (1)        |               | 1         |            |                           |                             |
| Adenocarcinoma (4)|       |           |            |                           |                             |
| Squamous cell carcinoma (1)| | | | | |
| RCC (2)         | 1             |           | 1          |                           |                             |
| Urinary tumor (5)|               |           |            |                           | 1                           |
| M : 5           |               |           |            |                           |                             |
| Urothelial carcinoma (1)| | | | | |
| Bladder cancer (1)|         |           |            |                           |                             |
| Prostate cancer (1)|         |           |            |                           |                             |
| Nasal cancer (1)|               |           |            |                           | 1                           |
| M : 1           |               |           |            |                           |                             |

NSCLS: non-small-cell lung cancer; SCLS: small-cell lung cancer; RCC: renal cell carcinoma.
### Table 5: Treatment and prognosis of ICIs-GBS.

| Treatment                  | Recovery | Progression | Residual dysfunction | Death |
|-----------------------------|----------|-------------|----------------------|-------|
| IVIG (n = 3)                | 2        | 1           |                      |       |
| IVIG+steroid (n = 16)       | 8        | 4           | 2                    | 2     |
| IVIG+PLEX (n = 1)           | 1        | 1           |                      |       |
| IVIG+steroid+PLEX (n = 7)   | 2        | 2           | 3                    |       |
| Steroid (n = 5)             | 1        | 1           | 1                    |       |
| Steroid+PLEX (n = 1)        | 5        | 11          | 2                    | 9     |
| Total                       | 13       | 13          | 11                   | 9     |

IVIG: intravenous immunoglobulin; PLEX: plasma exchange.

The remaining cases, only the GBS subtype was mentioned. 54.5% (18/33) of cases were consistent with AIDP [16–19, 21, 22, 24, 26–30, 33, 34, 39, 42] and axonal damage accounted for 12.1% (4/33, AMSAN: 3 and AMAN: 1) [15, 23, 25, 27]. The subtypes in four cases were equivocal because they showed mixed features of axonal injury and demyelination [23, 31, 35, 36]. There were also three cases, two with MFS [13, 20] and the other with MFS-GBS overlap [32]. Regrettably, there were two cases of GBS diagnosis with no mention of subtypes [13, 38, 40].

CSF analysis was performed in 31 out of the 33 cases. The average protein level of CSF in patients with GBS related to ICIs was 180.68 ± 152.51 mg/dl (range: 37-680 mg/dl). 63.6% of the cases (21/33) presented with typical albuminocytological dissociation (cells ≤ 5/μl and CSF protein > 45 mg/dl) [14, 16, 20–22, 24, 28, 30–34, 38, 40–42]. The median value of CSF protein was 124.5 mg/dl (range: 73-680 mg/dl). Slight pleocytosis (i.e., cell count > 5/μl) was detected in 4/33 cases (12.1%) with a maximum cell count of 15/μl and a median CSF protein of 115 mg/dl [15, 19, 27, 37]. CSF protein values and cell counts were normal in three cases [23, 25, 35], and there was elevated CSF immunoglobulin G levels in one case [25].

MRI was performed in 54.5% (18/33) of cases, of which both brain and spinal cord were examined in 8 cases and only spinal cord was 10 cases. MRI results showed nerve root involvement in 4 cases [16, 27, 29, 31], severe spinal stenosis in 1 case [19], cranial nerve involvement in 1 case, and normal or no metastatic signs in the rest [29].

### 3.5. Treatment and Prognosis of GBS

Twenty-seven cases (81.8%) were treated with intravenous immunoglobulin (IVIG), sixteen of the 27 patients with a combination of steroid therapy and one with PLEX. Seven of the 27 patients were treated with all three treatments. Five cases were treated with steroid therapy alone, and one case was treated with steroid combined with PLEX. No patients were treated with PLEX alone.

After treatment, 24 cases (72.7%) recovered or had only mild residual dysfunction, with two of them rechallenged ipilimumab [14] or pembrolizumab [21], and 5 cases had residual mild paresthesia [13, 14, 26, 29, 33]. Among the 33 ICIS-related GBS patients, 5 patients developed tumor progression after discontinuation of ICIS treatment, including 4 patients with melanoma [14, 31, 32, 37] and 1 patient with bladder cancer [22]. Of the eight deaths, three died of the respiratory muscle paralysis caused by GBS [17, 38, 41], 2 died of infection [13, 39], and three were due to progression of the tumor caused by ICI discontinuation [16, 28, 40].

### 4. Discussion

The effects of checkpoint inhibition affect a wide range of system and trigger a wide range of autoimmune toxicity. The exact mechanism of neurological irAEs in ICI-treated patients is unknown [44]. The existence of shared antigens between the tumor and itself may be one possible mechanism, such as gangliosides found in both melanoma and Schwann cells [45]. ICI-related GBS is rare as a type of neurological irAEs, but it can develop into life-threatening consequence once occurred. Diagnosis of ICI-related GBS should be made in the shortest possible time so as not to delay the administration of immune-regulation therapy.

There was a male preponderance in 33 ICI-related GBS patients we collected, with 3.71 times as many cases as female (male 26 and female 7). However, among GBS triggered by infection, males were affected only 1.5 times more frequently than females [11]. An epidemiological study on the risk factors of melanoma showed that the incidence of melanoma of men was almost three times that of by women by the age of 75 [12]. The incidence of lung tumor in men has historically been higher than in women, although the incidence of lung tumor in women has risen since the 1960s, especially in younger women [46–48]. Perhaps the higher incidence of cancer in men, resulting in more opportunities for men to use ICIs, was one of the reasons for the higher incidence of ICI-related GBS. Besides, ICIS were more effective for male cancer patients than female patients [49]. And the development of irAEs was related to the beneficial effects of immunotherapy in malignant tumors, especially in advanced-stage melanoma, advanced and metastatic NSCLC, and advanced renal cell carcinoma (RCC) [50]. The high effectiveness of ICI treatment in male patients may be also responsible for the male preponderance in ICI-related GBS.

In this study, melanoma had the largest number of tumor type that caused GBS after ICI treatment. Neurological irAEs were rare, with an incidence of less than 3% [8], whereas the overall incidence of severe nerve injury in melanoma patients treated with nivolumab with or without ipilimumab reached 0.93% [7], nearly one-third of the total neurological irAEs. Well know, GBS is a multifactorial autoimmune disorder, cell-mediated immunity plays an important role in immunopathology of all types of GBS. The activation of T cell caused by bacterial and virus leads to the production of cytokines and the release of free radicals, thus resulting in segmental demyelination [51]. And the cross-reaction between B-cell autoantibodies and axon gangliosides leads to axonal degradation [51]. Melanocytes and Schwann cells originate from the neural crest and have many common epitopes in humoral and cellular immune responses [52]. T cells regulate the degree of initial response of T cells by upregulating CTLA-4, while PD-1 inhibits the response of T cells in peripheral...
tissues and plays an important role in immune self-tolerance [53]. Due to the cross-reaction of molecular mimicry, T cell-mediated autoimmunity against melanoma cell antigens may also have an effect on the myelin antigens on Schwann cell membranes. In addition, the response rate of melanoma to ICIs was higher than other tumors [54]. A FAERS database-based clinical study also showed that patients with melanoma or non-small-cell lung cancer maybe at higher risk of fatal neurologic AEs [55]. Therefore, the author speculated that melanoma patients were more likely to develop GBS after ICI treatment than other types of tumors.

Existing reports suggested that the overall incidence of neurological adverse events (nAEs) at all levels was 3.8% for anti-CTLA-4 and 6.1% for anti-PD-1/PD-L1 [56]. CTLA-4 and its ligands are only expressed on immune cells, while PD-1 and PD-L1 (ligands of PD-1) are expressed on both immune and nonimmune cells in peripheral tissues [57]. The difference in spatial distribution between the CTLA-4 and PD-1 pathways may explain the high incidence of GBS in patients treated with nivolumab.

Many literatures had reported the timing of irAEs onset after the initiation of ICI treatments. The skin manifestations appeared at 2-3 weeks, and immune-mediated colitis, hepatitis, pneumonitis, and nephritis appeared approximately 5-10 weeks, 12-16 weeks, 8-14 weeks, and 14-42 weeks, respectively. Endocrine dysfunctions appeared from 9 weeks [58]. At present, there is no literature on the time to onset of neurologic symptom related to GBS caused by ICIs. The initial time of symptoms in 33 patients in this article was analyzed, and the results suggested that the median time was 8.2 weeks after the initiation of ICI treatments. Compared with GBS caused by infectious triggers, neurologic symptom appeared much later. This conclusion was expected to be helpful for the rapid diagnosis of ICIs-GBS.

Of the 33 GBS related to ICI patients we collected, the initial symptoms were very similar to infection-triggered GBS. Lumbar puncture was performed, and CSF analysis revealed elevated protein levels and albuminocytologic dissociation. A study of 962 patients with infection-induced GBS showed that the average protein level was 113.8 ± 11.8 mg/dl (range: 18–450 mg/dl) [59]. In this study, the average protein level of CSF in patients with GBS related to ICIs was 180.68 ± 152.51 mg/dl (range: 37-680 mg/dl). From a numerical point of view, the levels of CSF protein level of ICI-related GBS seemed to be higher than those of GBS induced by infection. Although it was not possible to distinguish infection-induced GBS from ICI-induced GBS based on CSF protein levels, lumbar puncture and protein-cell-separation were valuable in differentiating a variety of diseases such as spinal cord compression, metabolic diseases, side effects of drugs, vasculitis, and chronic inflammatory demyelinating polyneuropathy. In addition to elevated protein levels, lymphocytosis may also occur [37]. A similar pattern was observed in this study, with 4 patients showing a mild lymphocytosis in the CSF. However, multiple cases had been reported of lymphocytosis in the CSF of patients with infection-induced GBS [60–63]. Obviously, lymphocytosis in the CSF was not a characteristic of ICI-related GBS.

The electrophysiological results detailed in this study indicated that ICI-related GBS was a generalized, sensorimotor polyneuropathy characterized by mixed axonal/demyelination. An electrophysiological study of ICI-related peripheral neuropathy showed that immune-mediated neuropathy mainly manifested as demyelination of motor nerves, followed by length dependent axonal loss in sensory nerve [60]. The results of this study were in part consistent with the above conclusions. No matter what kind of electrophysiological changes were closely related to the autoimmune response of ICIs against peripheral nerve tissue, the onset of symptoms of neuromyopathy was closely related to ICI treatment, and corticosteroid or immune-regulatory therapy had good results.

In the treatment of all 33 patients, the immediate discontinuation of ICIs was an uncontroversial decision. Most patients received IVIG after discontinuation, with 16 patients receiving both IVIG and steroid therapy. Despite steroids were generally not recommended for treatment in infection-induced GBS, in ICI-related GBS, both American Society of Clinical Oncology (ASCO) Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN) guidelines stated that trial of (methyl) prednisolone 1-2 mg/Kg was reasonable [64, 65], especially when CSF pleocytosis was higher than being anticipated for GBS [10]. And if the symptoms deteriorated, plasma exchange or IVIG treatment could be considered [66].

Among the 33 ICI-related GBS patients, 5 patients developed tumor progression after discontinuation of ICI treatment. One of the four patients with progressed melanoma rechallenged different class of immunotherapy, with significant and sustained response nearly 1 year later and no recurrence of GBS-like neuropathy. Whether or not to retreat with ICIs and whether to retreat with the same or different ICIs are challenges for oncologists. There is also limited data on the clinical efficacy and safety of retreatment. The current guidelines suggested that corticoid therapy and temporary or permanent discontinuing ICIs were required for grade ≥ 2 irAEs and permanently discontinuing ICI treatment for grade 4 irAEs [65, 67]. A study had shown that the recurrence rate of the same irAEs resulting in discontinuation of ICI treatment in cancer patients who rechallenged the same ICI was 28.6% (anti-PD-1 or anti-PD-L1 monotherapy), 47.4% (anti-CTLA-4 monotherapy), and 43.5% (combination therapy), respectively [66]. The recurrence rate of irAEs varied depending on the organ involved in the initial irAEs, with gastrointestinal irAEs having the highest recurrence rate [68]. And the variables associated with a higher recurrence rate of irAEs were anti-CTLA-4 regimen, age, colitis, hepatitis, and pneumonia, in order [68]. In addition, the duration from ICI discontinuation to rechallenge, and the severity of the initial irAEs did not predict whether irAEs would reappear after rechallenge of ICIs [69]. However, no relevant literature has been reported on whether discontinuation due to ICI-related GBS can rechallenge the same or different ICIs again.

In addition, paraneoplastic peripheral neuropathy should be excluded in the diagnosis of ICI-related GBS. Paraneoplastic peripheral neuropathy is a remote effect of the malignancy
mediated by the immune system. It develops prior or during a cancer and is independent of tumor infiltration or cancer therapy [70]. Paraneoplastic sensory neuropathy is the most frequent in this group of disorders, and motor, autonomic, or central nervous systems are also involved [71]. Date on the treatment of paraneoplastic peripheral neuropathy is limited, and the combination of malignancy therapy with immunomodulatory therapies such as corticosteroids, IV immunoglobulin, or immunosuppressants may be effective [72]. However, ICI-related GBS occurred in malignant tumors after ICI treatment, and the immunomodulatory therapeutic effect was obvious. This is the most obvious difference between the two.

Here are also several limitations in this study. First, the number of the included cases was small which limited us to perform subgroup analysis. Second, patients with various cancers were included, which might have bias in the incidence of some adverse effects.

5. Conclusion

Elderly male patients with melanoma were most likely to develop ICI-related GBS. And the median duration was 8.2 weeks after the initial ICI treatment. In order to make a final diagnosis, physicians need to collect specific neurological symptoms and signs and combine them with CSF analysis and electrophysiological examination. In addition, imaging is required to exclude tumor metastasis. Immediate termination of ICIs followed by IVIG in combination with high-dose steroids therapy or PLEX and supportive treatment could lead to a better prognosis.

Abbreviations

ICIs: Immune checkpoint inhibitors
CTLA-4: Cytotoxic T lymphocyte-associated antigen-4
PD-1: Programmed cell death protein-1
PD-L1: Programmed cell death protein-1 ligand
irAEs: Immune-related adverse events
GBS: Guillain-Barré syndrome
AIDP: Acute inflammatory demyelinating polyneuropathy
AMAN: Acute motor axonal neuropathy
AMSAN: Acute motor and sensory axonal neuropathy
MFS: Miller fisher syndrome
DML: Distal motor latency
EMG: Needle electromyography
IVIG: Intravenous immunoglobulin
PLEX: Plasma exchange
CSF: Cerebrospinal fluid
CNS: Central nervous system
NSCLC: Non-small-cell lung cancer
RCC: Renal cell carcinoma.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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