Immune Checkpoint Inhibitor Associated Autoimmune Encephalitis, Rare and Novel Topic of Neuroimmunology: A Case Report and Review of the Literature

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Abstract: Immune checkpoint inhibitors (ICIs) are being used in patients with various advanced malignancies, and patient outcomes have improved considerably. Although ICIs can effectively treat tumors, 30–60% of patients experience immune-related adverse events (irAEs). Autoimmune encephalitis (AE) is a rare irAE that has become a novel topic in neuroimmunology and has received increasing attention in recent years. Herein, we report a rare case of GAD65-antibody–associated AE after metastatic small cell lung cancer treatment with pembrolizumab. The patient received IVIg therapy for AE and continuous pembrolizumab therapy without suspension of tumor treatment. At 1 year follow-up, both the patient’s AE symptoms and tumors were stable. We consider that the treatment of ICI-associated AE should be more individualized with prudent decision-making and should balance the tumor progression and AE treatment. In addition, we have also comprehensively reviewed the literature of ICI-associated AE, and summarized the clinical features, treatment, and prognosis of AE caused by ICI, thus broadening our understanding of the neurological complications caused by ICI.

Keywords: immune checkpoint inhibitors; immune-related adverse event; autoimmune encephalitis; pembrolizumab

1. Introduction

Immune checkpoint inhibitors (ICIs) are a class of monoclonal antibodies that target regulatory immune checkpoint molecules that inhibit T cell activation. ICIs can enhance T cell-mediated anti-tumor immunity and promote immune-mediated tumor cell clearance by blocking co-inhibitory signaling pathways [1–3]. Their antitumor effects have been recognized in clinical trials and have been approved by the FDA for the treatment of malignant tumors, such as melanoma, non-small cell lung cancer, colorectal cancer, and hepatocellular carcinoma [4].

ICIs can be divided into monoclonal antibodies against CTLA-4 and monoclonal antibodies against PD-1/PD-L1 depending on the pathways they act on [5]. Monoclonal...
antibodies against PD-1/PD-L1 are the favorable method for modern immunotherapy of solid tumors [6–8]. ICIs can enhance the anti-tumor immune response by removing the inhibitory effect of PD-1 or PD-L1 immune checkpoints on the activation and proliferation of T cells, and reduce the number and/or inhibitory activity of Treg cells [9]. By doing so, the killing function of T cells against the tumor is restored, leading to the inhibition of tumor development [1]. However, when ICIs induce activation of the immune system, they also nonspecifically lead to the destruction of the immune homeostasis of non-tumor tissues, resulting in severe immune and inflammatory reactions. These include clinical immune-related adverse events (irAEs) [10,11]. At present, the specific mechanism of irAE generation is not clear, and it is generally believed to be related to the disorder of immune homeostasis caused by ICI treatment [12,13]. There are large amounts of ICs on the surface of non-tumor cells; ICI combined with them can lead to the activation of complement in the body and increase the level of inflammation, thereby disrupting immune homeostasis [14].

Common irAEs include skin rash, itching, colitis, hepatitis, and all types of endocrine diseases [15]. Nervous system irAEs are relatively rare, which include central nervous system (CNS) irAEs and peripheral nervous system (PNS) irAEs. PNS irAEs mainly include myasthenia gravis, Guillain–Barre syndrome, and peripheral sensory motor neuropathy [16]. CNS irAEs are much rarer than PNS irAEs. ICI-associated autoimmune encephalitis (AE) is an uncommon complication that has rarely been reported [17,18], and thus not completely understood. Herein, we report the first case of pembrolizumab-associated GAD65 antibody AE with a favorable short-term prognosis after treatment. Furthermore, in order to better understand the CNS complications caused by ICI, we comprehensively reviewed ICI-associated AE.

2. Materials and Methods

References for the review were identified by searching English literature in the PubMed database published from 2016 to 2022, using the search terms (alone or in logical combinations): “immune checkpoint inhibitor”, “autoimmune encephalitis”, “immune-related adverse events”, “anti PD1”, “anti PDL1”, and “anti CTLA4.” The inclusion criteria are as follows: patients with (1) encephalitis symptoms identical to classical AE, regardless of whether neuronal autoantibodies were detected; (2) any AE symptoms associated with classic tumor neuronal autoantibodies; or (3) symptoms associated with autoantibodies against synaptic receptors or other neuron cell surface proteins after ICI treatment. Patients were excluded if neuronal autoantibodies were detected before ICI treatment [19].

3. Case Report

A 51-year-old man was admitted with an unsteady gait and slurred speech, which persisted for 20 days. He had undergone pulmonary nodule resection in April 2019. Frozen section pathology revealed small-cell carcinoma in the anterior segment of the right upper lobe. He received multiple doses of VP-16, carboplatin, chemotherapy, and radiotherapy from May 2019 to November 2020. In January 2021, positron emission tomography-computed tomography (PET-CT) revealed two round and low-density lesions with increased fluorodeoxyglucose (FDG) metabolism on the right liver lobe, enlarged lymph nodes with FDG hypermetabolism in the retroperitoneal area and the space between the right kidney and pancreas. The size of lesions on the right lobe of the liver were 1.3 × 1.1 cm and 1.34 × 1.44 cm. Considering the liver and lymph node metastases, on the 3rd and 25th of February 2021, the patient received pembrolizumab therapy. On 15 April 2021, he developed slurred speech and an unsteady gait. The patient was again treated with pembrolizumab on the 29 of April 2021, and his symptoms progressed significantly and his modified Rankin Scale (mRS) score deteriorated to 4. Neurological examination revealed dysmetria on the finger-to-nose test, positive Romberg’s sign, ataxic gait, and nystagmus. The cranial nerves were intact and there was no nuchal rigidity. The patient had normal muscle strength, muscle tone, and tendon reflexes. Cerebrospinal fluid (CSF) analysis showed normal opening pressure (120 mmH₂O), nucleated cell count 2 × 10⁶/L, protein
514.45 mg/L, chloride 128 mmol/L, and sugar 2.96 mmol/L. Cranial magnetic resonance imaging (MRI) showed evidence of mild cerebellar atrophy (Figure 1A,B). \(^{18}\)F-FDG-PET-CT indicated decreased metabolism in both cerebellar hemispheres.

The autoimmune encephalitis antibody panel revealed that anti-GAD65 and anti-SOX1 antibodies were present in both serum and CSF, while other antibodies were absent. The titers of GAD65 and SOX1 antibodies in the serum were 1:30 and 1:10, respectively; and while they were 1:100 and 1:10, respectively, in the CSF. Therefore, the patient was diagnosed with pembrolizumab-associated AE. The irAE grade was 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE-5.0) [20]. The patient was given intravenous immunoglobulin (IVIg) at 0.4 g/kg/day for 5 days, and his speech and gait improved significantly. His mRS improved to 1. Considering that excessive immunosuppressive therapy might lead to tumor recurrence, this patient did not receive glucocorticoid or immunosuppressive therapy. Furthermore, pembrolizumab treatment was continued for the tumor. He received IVIg therapy 3 months later to prevent the recurrence of AE symptoms. At the 1-year follow-up, his AE symptoms had largely recovered, and the tumor was stable. The titer of GAD65 antibodies in serum decreased to 1:1. CT showed that the size of the metastases in the right lobe of the liver were 0.3 \(\times\) 0.51 cm and 0.67 \(\times\) 0.88 cm. The retroperitoneal lymph nodes and lymph nodes in the right renal space between the pancreas were also reduced (Figure 1C, timeline for this patient).

**Figure 1.** Mild cerebella atrophy evidence on sagittal and axial brain MRI (A,B). The timeline of the patient (C).
4. Discussion

4.1. Pembrolizumab-Associated GAD65 Antibody AE, a Very Rare Complication of ICI

The incidence of irAEs in the nervous system after ICI treatment is 2% to 6% [21,22], of which the incidence of encephalitis is 0.05% [16]. As far as we know, ICI-associated AE is currently limited to a single case report or a few small case series [18,23]. Cases of ICI-associated AE with autoantibodies are very rare. This is the first case of pembrolizumab-associated GAD65 antibody-positive AE. We noticed that this patient experienced a reduction in tumor size and progression of ataxia with GAD65 and SOX1 autoantibodies after pembrolizumab treatment, which indicated a diagnosis of pembrolizumab-associated AE [19]. In this patient, pembrolizumab was very effective in the treatment of tumors; both the tumor size in the lung and tumor metastasis were well controlled after the treatment. In addition, after five days of IVIg treatment, the patient’s AE symptoms improved significantly, and we resumed the pembrolizumab treatment. At 1-year follow-up, both the patient’s AE symptoms and tumors were stable. In previous reports, steroids rather than IVIg were generally chosen for ICI-associated AE [24], and ICI treatment was usually discontinued. However, in our patient, timely and effective immunotherapy and continued treatment with pembrolizumab resulted in significant reduction of both AE and tumors. Our case may provide new directions for future treatment of ICI-associated AE.

4.2. Literature Review of ICI-Associated AE

By reviewing the literature, we found 50 cases of ICI-associated AE; of which, 28 and 22 cases were with and without autoantibodies, respectively. Patients’ age ranged from 19 to 81 years, with a mean age of 61.5 years, with a male-to-female ratio of 1:1. The patients had lung cancer (20), melanoma (12), renal cancer (6), pleural mesothelioma (3), Hodgkin’s lymphoma (2), ovarian cancer (1), breast cancer (1), endometrial cancer (1), uterine cancer (1), Merkel cell carcinoma (1), thymic carcinoma (1), and urothelial carcinoma (1). Thirty-nine patients were explicitly prescribed with ICI-specific drugs: Nivolumab (15), ipilimumab/Nivolumab (11), Pembrolizumab (7), Sintilimab (1), Durvalumab (2), Dostarlimab (1), and Atezolizumab (2). After the use of ICI, the patients presented with AE. The time from ICI use to AE symptom onset ranged from 4 days to 18 months (median, 3 months). Examination of CSF showed increased an cell number in 21 patients, increased protein in 35 patients, and a positive oligoclonal band (OCB) in 7 patients. Twenty-eight patients were found to have positive autoimmune antibodies in the cerebrospinal fluid or serum, including Ma2 Ab (10), GAD Ab (7), Hu Ab (3), NMDAR Ab (4), SOX1 Ab (2), Ri Ab (1), GABAbR Ab (1), and CASPR2 Ab (1) [25]. Hu Ab and NMDAR Ab were double-positive in one patient [26]. According to CTCAE-5.0, there were 3 Grade 2 cases, 29 Grade 3 cases, and 15 Grade 4 cases [20]. After treatment with steroids, IVIg, plasma exchange, and rituximab, the symptoms of encephalitis improved in 31 patients; 13 patients did not improve, and 6 patients died (Table 1).
| Author       | ICI                        | Age | Sex | Onset Time | Cancer                  | Antibody (CSF/Serum) | Symptoms and irAEs Grade | CSF (White Cells/Protein/OCB) and MRI | Treatment                              | Prognosis       |
|--------------|----------------------------|-----|-----|------------|-------------------------|----------------------|---------------------------|----------------------------------------|----------------------------------------|-----------------|
| Brown [27]   | Pembrolizumab              | 67  | M   | 7 M        | Melanoma                | CASPR2 Ab(+/-)       | Short-term memory loss, anxiety episodes, G3 | T2 hyperintensity of the MTL bilaterally | steroid                  | partially improved |
| Kopecky [28] | Nivolumab                  | 64  | M   | 3 M        | Renal cancer            | Ma2 Ab(+/-)          | Uncontrollable movements, choreiform movements, G3 | N/N/NA increased signal within the basal ganglia | steroid, infliximab | deceased         |
| Shah [29]    | Nivolumab                  | 44  | F   | 4 M        | Lung adenocarcinoma     | GAD Ab(+/-)          | Dysarthria, dyskinesias, refractory seizures, G4 | T2 signal hyperintensities of the bilateral MTL compatible with limbic encephalitis | ICIs discontinued, steroid, PLEX, rituximab | partially improved |
|              | Nivolumab                  | 66  | F   | 4 M        | Lung cancer             |                       | Dysarthria, dysarthric, dyskinesias, bilateral arm and leg ballismus, G3 | symmetric T2 hyperintense and T1 hypointense basal ganglia abnormalities | ICIs discontinued, steroid, IVlg, rituximab | deceased         |
| Williams [17]| Ipilimumab/Nivolumab       | 56  | F   | 18 D       | Melanoma                | NMDAR Ab(+/-)        | Disorientation, inattention, bradykinesia, hyperreflexia, G3 | 1/N/NA stable encephalomalacia at sites of prior radiosurgery with no additional metastases | ICIs discontinued, steroid, IVlg, rituximab | partially improved |
| Gill [26]    | Pembrolizumab              | 71  | F   | 3 M        | Lung adenocarcinoma     | Ri Ab(+/-)           | Short-term memory loss, progressive difficulty ambulating, G3 | new nonspecific T2 hyperintensities in the right MTL | ICIs discontinued, steroid                  | improved         |
| Shibaki [30] | Nivolumab                  | 78  | M   | 9 D        | Pleural mesothelioma    | Hu Ab(+/-), NMDAR Ab(+/-) | Progressively altered mental status, truncal ataxia, vertical nystagmus, G3 | 1/1/NA T2/FLAIR hypersignal involving the uncus bilaterally, periventricular regions of the third ventricle and hypothalamus | ICIs discontinued, steroid, rituximab | not improved     |
| Vogrig [23]  | Pembrolizumab              | 79  | M   | 2 M        | Lung cancer             | Ma2 Ab(NA/NA)        | Impulsivity and disinhibition, hyperphagia, confusion, decreased consciousness, G4 | N/1/NA FLAIR bilateral MTL hypersignal | ICIs discontinued, steroid, PLEX, rituximab | not improved     |
|              | Ipilimumab/Nivolumab       | 71  | M   | 5 M        | Pleural mesothelioma    | Ma2 Ab(+/-)          | Narcolepsy-cataplexy, hyperphagia, psychiatric symptoms, G3 | 1/1/NA FLAIR signal involving the uncus bilaterally, periventricular regions of the third ventricle and hypothalamus | ICIs discontinued, steroid, rituximab | not improved     |
|              | Nivolumab                  | 57  | F   | 8 M        | Pleural mesothelioma    | Ma2 Ab(+/-)          | Memory deficits, epilepsy, psychomotor retardation, G4 | NA/1/NA FLAIR bilateral MTL hypersignal | ICIs discontinued, steroid, IVlg, rituximab | not improved     |
|              | Pembrolizumab              | 47  | M   | 8 M        | Lung cancer             | Ma2 Ab(+/-)          | Ophthalmoplegia, head drop, G3 | N/1/NA FLAIR bilateral MTL hypersignal | ICIs discontinued, Steroid | not improved     |
|              | Nivolumab                  | 55  | M   | 3 M        | Kidney cancer           | Ma2 Ab(+/-)          | Right ear hearing loss, ataxia, vertigo, memory deficits, G3 | N/1/NA FLAIR bilateral MTL hypersignal | ICIs discontinued, Steroid, PLEX | not improved     |
| Author        | ICI                  | Age | Sex | Onset Time | Cancer                  | Antibody (CSF/Serum) | Symptoms and irAEs Grade                                                                 | CSF (White Cells/Protein/OCB) and MRI                  | Treatment       | Prognosis       |
|---------------|----------------------|-----|-----|------------|-------------------------|-----------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------|----------------|-----------------|
| Nivolumab     | 69 M                 | 3 M |     | 3 M        | Kidney cancer           | Ma2 Ab(+/-)           | Confusion, focal seizures, G3                                                       | N/+ /NA FLAIR bilateral MTL hypersignal                | ICI discontinued, Steroid | not improved    |
| L. Fellner    | [31] Nivolumab       | 26  | F   | NA         | Hodgkin lymphoma        | Ma2 Ab(-/+ )          | Seizures, G4                                                                         | N/N/NA FLAIR signal changes in MTL                    | ICI discontinued, Steroid | improved        |
| Ipilimumab/Nivolumab | 19 F NA | Melanoma | NMDAR Ab(+/-) | Progressive short-term memory loss, seizures, G4 | N/N/NA fluid-attenuated inversion recovery hyperintensities involving the MTL and hippocampi bilaterally | ICI discontinued, steroid, IVIg | deceased        |
| N. Shah [32]  | Pembrolizumab        | 70  | M   | 17 M       | Melanoma                | NMDAR Ab(+/-)         | Hypoactive delirium, recurrent falls, brief witnessed tonic-clonic seizures, G4     | N/N/NA Normal                                         | ICI discontinued, steroid, IVIg | not improved    |
| Chung [18]     | Ipilimumab/Nivolumab | 36  | F   | 2 M        | Thymoma                 | GAD Ab(+/-N)          | Progressive short-term memory loss seizures, G4                                     | N/N/NA fluid-attenuated inversion recovery signal intensity in the temporal lobes, frontal lobes, brainstem, including bilateral limbic structures and left temporal cortex | ICI discontinued, steroid, IVIg | deceased        |
| Nivolumab     | 56 F 3.5 M           | Renal cancer | Ma2 Ab(+/-) | Seizure, memory loss, behavioral and personality changes, left internuclear, ophthalmoplegia, G4 | N/1/NA multiple areas of increased T2 fluid-attenuated inversion recovery signal intensity in the temporal lobes, frontal lobes, brainstem, including bilateral limbic structures and left temporal cortex | ICI discontinued, steroid, IVIg, mycophenolate mofetil | not improved    |
| Kang [34]     | Sintilimab           | 66  | F   | 3 M        | SCLC                    | Hu Ab(+/-N)           | Focal seizures, G3                                                                  | ↑/N/NA NA                                             | ICI discontinued, steroid | partially improved |
| Hottinger [35]| Ipilimumab/Nivolumab | 71  | F   | 4 M        | SCLC                    | Hu Ab(+/-N)           | Memory deficits, G2                                                                  | ↑/N/NA NA                                             | ICI discontinued, steroid, Natalizumab | partially improved |
| Pieperas [36]| Ipilimumab/Nivolumab | 52  | F   | 2 W        | Melanoma                | GAD Ab(+/-)           | Short-term memory loss, cognitive dysfunction, limb ataxia, epileptic seizures, G4 | ↑/1/NA small alterations                             | ICI discontinued, steroid, infliximab, reuse nivolumab | deceased        |
| Burke [37]    | Nivolumab            | 64  | F   | 4 M        | Ovarian clear cell cancer | GAD Ab(-/-)           | Fever, stiff arms and legs, occasional spasms, G3                                   | N/N/NA/Normal                                          | Steroid, PLEX               | partially improved |
| Duong [38]    | Nivolumab            | 57  | M   | 5 W        | SCLC                    | GAD Ab(-/+ )          | NA                                                                                   | ↑/N/NA FLAIR signal in MTL                             | Steroid, IVIg               | deceased        |
| Nivolumab     | 64 M 6 M             | SCLC | SOX1 Ab(+/-) | NA |                                  | ↑/N/+ NA                  | Steroid, IVIg                                                                 | ↑/N/NA FLAIR signal in temporal lobes and thalami      | Steroid | partially improved |
| Ghouse [39]   | Ipilimumab/Nivolumab | 71  | F   | 18 M       | NSCLC                   | NA                     | Slurred speech, word-finding difficulty, ataxia, lower extremity hyperreflexia, G3 | N/1/+ Normal                                           | Steroid | partially improved |
| Author            | ICI                        | Age | Sex | Onset Time | Cancer                  | Antibody (CSF/Serum) | Symptoms and irAEs Grade                                    | CSF (White Cells/Protein/OCB) and MRI | Treatment                        | Prognosis                |
|-------------------|----------------------------|-----|-----|------------|--------------------------|-----------------------|-----------------------------------------------------------|-------------------------------------|----------------------------------|--------------------------|
| Maniscalco [40]   | Nivolumab                  | 63  | M   | 3 M        | Melanoma                 | GAD Ab(+/-)           | seizures, memory loss, behavioral changes, walking difficulties, G4 | ↑/N/+ limbic involvement             | ICI discontinued, steroid, IVIg | not improved             |
| Shechtman [41]    | Durvalumab                 | 66  | F   | 2 M        | SCLC                     | GABAbr Ab(+/-)        | Seizures, disorientation, memory disturbances, G4         | N/N/NA mild chronic microvascular ischemic changes | Steroid                          | partially improved        |
| Yorduangjun [42]  | Dostarlimab                | 52  | F   | NA         | Endometrial cancer       | NMDAR Ab(NA/NA)       | Confusion, tremors, loss of fine motor skills, G3         | ↑/↑/↑ right temporal sclerosis       | ICI discontinued, steroid, IVIg, rituximab | partially improved        |
| Taliansky [24]    | Anti CTLA4                 | 70  | M   | 20 D       | SCLC                     |                       | Seizures, speech disturbances, G4                         | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1                   | 87  | M   | 12 D       | Urothelial carcinoma    |                       | Confusion, G3                                             | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | not improved              |
|                   | Anti CTLA4+anti PD1        | 49  | F   | 9 D        | Uterine carcinoma       |                       | Cerebellar ataxia, opsinolus, tremor, G3                   | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1                   | 71  | F   | 24 D       | Breast cancer           |                       | Psychotic state, G3                                       | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1                   | 84  | M   | 21 D       | Melanoma                |                       | Confusion, somnolence, G2                                 | NA/N/↑ NA Normal                    | NA, ICI discontinued            | partially improved        |
|                   | Anti PD1                   | 59  | M   | 210 D      | Melanoma                |                       | Confusion, somnolence, headache, G2                       | NA/↑/↑ NA Normal                    | NA, change the ICI type        | partially improved        |
|                   | Anti PD1                   | 71  | F   | 110 D      | NSCLC                   |                       | speech and behavioral disturbance, generalized and complex partial epileptic event, G3 | NA/↑/↑ NA Abnormal                  | ICI discontinued, NA            | not improved              |
|                   | Anti PD1                   | 68  | M   | 150 D      | NSCLC, adenocarcinoma   |                       | Confusion, generalized epileptic event, G4                 | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1                   | 67  | F   | 15 D       | NSCLC, adenocarcinoma   |                       | Confusion, sensory neuropathy, G3                         | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1+anti LAG3         | 67  | F   | 11 D       | Melanoma                |                       | Ataxia, speech disturbances, partial seizure, G3          | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
|                   | Anti PD1                   | 73  | F   | 15 D       | Renal cancer            |                       | Headache, confusion, G3                                   | NA/↑/↑ NA Normal                    | ICI discontinued, NA            | partially improved        |
| Yamaguchi [43]    | Atezolizumab               | 56  | M   | 17 D       | Lung cancer             |                       | Consciousness disturbance, motor aphasia, G3              | 1/↑/↑ NA Normal                     | ICI discontinued, steroid       | partially improved        |
| QUACH [44]        | Pembrolizumab              | 69  | M   | 2 M        | Melanoma                |                       | Headaches, fever, and altered mental status, G3           | N/↑/↑ NA suspected left vertebral artery occlusion, known cavernous venous malformation, chronic right optic nerve atrophy | ICI discontinued, steroid     | improved                  |

Table 1. Cont.
| Author       | ICI               | Age | Sex | Onset Time | Cancer      | Antibody (CSF/Serum) | Symptoms and irAEs Grade | CSF (White Cells/Protein/OCB) and MRI | Treatment                      | Prognosis         |
|--------------|-------------------|-----|-----|------------|-------------|----------------------|--------------------------|----------------------------------------|----------------------------------|------------------|
| Braden [45]  | Ipilimumab/Nivolumab | 61  | M   | 7 M        | Melanoma    |                      | Sudden onset aphasia, left lower limb myoclonic jerks, confusion, G3 | FLAIR hyperintensity in the right MTL with differentials including encephalitis or postictal changes | ICIs discontinued, steroid                  | partially improved |
| Nishijima [46]| Atezolizumab      | 72  | F   | 7 M        | NSCLC       |                      | Gait disturbance, mild disturbance of consciousness, G3             | N/N/↑/NA symmetrical high signal in the thalamus bilaterally | steroid, IVIg                        | not improved     |
| Shionoya [47]| Durvalumab        | 68  | F   | 1 M        | SCLC        |                      | disorientation, memory impairment, eating difficulty, G3            | ↑/↑/↑/Normal symmetrical high signal in the thalamus bilaterally | ICIs discontinued, Steroid                | improved          |
| NIKI [48]    | Pembrolizumab     | 51  | M   | 6 M        | NSCLC       |                      | seizure, difficulty in walking and communicating, G4               | ↑/↑/↑/Normal a tumor in the right frontal lobe of the brain | ICIs discontinued, Steroid                | partially improved |
| Nalbantoğlu [49]| Nivolumab      | 40  | M   | 1 M        | Hodgkin lymphoma |                      | disorientation, inattention, postural tremor in the upper left extremity, and ataxia G3 | ↑/↑/↑/↑ right occipital, left frontal millimetric lesions with gadolinium enhancement | ICIs discontinued, Steroid                | partially improved |
| Thouvenin [50]| Ipilimumab/Nivolumab | 70  | M   | 3 W        | Renal cancer |                      | Confusion, gait disturbance, aphasia, G3 | MRI was limited because of the patient’s agitation | ICIs discontinued, Steroid                | partially improved |
This table summarized the reported cases of ICI-associated AE (abbreviations: NA = not available, FLAIR = fluid-attenuated inversion recovery, MTL = mesial temporal lobe, OCB = oligoclonal band). We noticed that among the reported cases, only seven cases were related to the GAD65 antibody [51], ranging in age from 33 to 64 years. All patients developed neuropsychiatric symptoms after using nivolumab alone or in combination with ipilimumab; none have been reported for pembrolizumab with the GAD65 antibody. Among the seven patients, four had poor prognosis or died. Six patients suspended ICI immediately after the onset of AE symptoms. Piepgras et al. reported a patient whose treatment with nivolumab was continued after controlling symptoms with steroids and infliximab but died after the encephalitis symptoms recurred [36]. In contrast to the previously reported patient, our patient had a good prognosis at the 1-year follow-up. The prognosis of ICI-associated AE varied after treatment.

The mechanisms of ICI-associated AE may be due to the following reasons: (1) The immune response induced by ICI may cross-react with CNS autoantigens; (2) AE is closely associated with tumors [52]. ICI may simultaneously enhance the immune response of the tumor and the immune response to CNS; and (3) ICI may recognize innate immune molecules on the surface of neurons, and thus directly kill neurons through the complement system or cytotoxicity, leading to the release of intracellular antigens [53].

In addition to AE, ICI can also lead to other neurological complications. Neurological syndromes caused by ICI are mainly peripheral neuropathies, including myasthenia gravis [54], Guillain–Barre syndrome [55], chronic polyneuropathies [56], and mononeuropathies [57]. CNS complications include noninfectious encephalitis, demyelinating disease, and cerebral artery vasculitis [16]. Neurological complications associated with ICI treatment require medical attention.

4.3. Current Dilemma: The Balance between ICI Therapy, Tumor Progression, and AE Treatment

Immune-related adverse events are classified into five grades [20]. Due to the presence of pathogenic autoantibodies, the treatment of ICI-associated AE includes withdrawal of ICI, IVIg, plasma exchange, and immunosuppressive therapies. As discussed above, most scholars support stopping ICI therapy and initiating immunosuppressive therapy [58]. According to the principle of toxicity management, only Grade 1 irAEs could continue ICI. Grades 2–4 irAEs should withhold ICI and receive stronger immunosuppressive therapy [59]. However, discontinuation of ICI therapy may lead to tumor progression. In addition, strong immunosuppression is associated with tumor recurrence. Being able to balance the treatments may prove difficult. Based on our experience, the treatment of ICI-associated AE should be more individualized and prudent. We advocate that IVIg or plasma exchange may be the first choices for Grade 2 and Grade 3 patients, and ICI may not be discontinued at first. The patients need more close monitoring. If patients do not respond to first-line treatment or symptoms progression, ICI treatment needs to be suspended and stronger immunosuppressants can be used [60]. In the literature we reviewed, we found two Grade 2 patients who continued using ICI or were switched to another type of ICI, and had good prognosis [24]. However, because ICI-associated AE is a relatively new topic in neuroimmunology, we need more cases and multi-center research in the future.

5. Conclusions

This is the first case of pembrolizumab-associated AE with GAD65 and SOX1 antibodies, characterized by progressive cerebellar ataxia. It should be noted that this patient received IVIg therapy for AE and continuous pembrolizumab therapy without suspension of tumor treatment. At present, the treatment of ICI-associated AE needs to be more individualized with close monitoring, evaluation, and prudent decision-making. Finally, the mechanisms, clinical features, and treatment of ICI-associated AE are a new concept in the field of neuroimmunology, and further studies are needed.
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