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Review Article

Peripheral Nervous System Disorders Associated to Immune Checkpoint Inhibitors

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Abstract

Checkpoint inhibitors (ICI) are a monoclonal therapy, which act by blocking PD-1, PD-L1 and CTLA-4 molecules, responsible for immune control. Peripheral neurological system (PNS) are a varied and sometimes severe adverse event (AE) associated with its use. This review will explore the main presentations and possible severe complications in the PNS associated with ICI use.

Keywords: checkpoints inhibitors; peripheral nervous system; Guillain barre; Myastenia gravis

Introduction

Immune checkpoint inhibitors (ICI) are monoclonal antibodies that represent a new form of cancer treatment approved by a variety of cancers, like melanoma and lung cancer. They act by blocking immune checkpoints including cell death protein 1 (PD-1) and its ligand (PDL-1) and cytotoxic T lymphocytes associated antigen 4 (CTL4) [1,2]. The last one acts downregulating T lymphocytes activation by interaction with B7.2 expressed in antigen presenting cell (APC) and regulatory T cell (Treg)[2], while PD-1 and PD-L1, acts limiting T cell activation in peripheral tissues in contrast to CTL4[2].

This dysregulation of the immune system that brings immune response against cancer cells cause as well important immune related adverse events (AE).

The most commonly neurologic AE reported includes myasthenia gravis, encephalitis/meningitis and Guillain- Barre Syndrome[3,4,5]. Importantly, the association of ICIs is related with much more high-grade adverse events than mono therapy [6].

Although neurological AEs are not the most frequent AEs associated with ICI, they can cause severe or permanent neurological risk. Neurological AE together with cardiac AE represents half the cause of fatal AE in Wang and colleagues' retrospective analyses and 15% of the fatal AE from a global pharmacovigilance data [7,8]. Another important feature is that myocarditis that has the highest fatality rate among all adverse events, frequently co-occur with myositis (25%-32%) [9,10] and Myastenia gravis (MG) 25% [11].

Cases of serious AE related to the peripheral nervous system are evident in less than 1% of patients treated with ICI, among which the most frequent syndromes are immune mediated neuropathies and Guillain Barre syndrome [12]. Qianqian Fan study, for example, [13] analyzed reports from January 2004 to March 2020 from Food and Drug Administration Adverse Event Reporting System (FAERS), which 149 reports were screen out as GBS associated ICIs, which the outcome as hospitalization were 61,75% and death were 22,82%.

Therefore, for better understanding of rare AEs, this narrative review will provide up to date information about peripheral nervous system related to ICI therapy, treatment and prognosis

Peripheral Neuropathy

Neuropathies associated with ICI have an estimated incidence of 1% [2]. Other studies showed an incidence rate of 0.7%[3] and 1.28% [4] when relating neuropathy and immunotherapy. They may vary in severity from typical immune-mediated neuropathy as Guillain–Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) to the small-fiber sensory type (most commonly seen with chemo-therapies) [5–9]. Complications involving the peripheral nervous system (PNS) have been reported in patients treated with anti-PD-1/PD-L1 agents, anti -CTLA4 or using both of them combined. They have consisted in mild to moderate peripheral neuropathies [8–10].

In the study by Dubey *et al* (2014), in which 19 patients with neuropathies relate AE were identified, the phenotypes associated with ICIs. Were, more prevalently, cranial neuropathy with or without meningitis (7) and polyradiculoneuropathies (6).

The mean time to the start of immunotherapy therapy and the onset of symptoms of neuropathy was 9 weeks. The same study also carried out an analysis comparing ICI-related neuropathy with neuropathies associated with cytotoxic chemotherapies and it was possible to note that melanoma was the type most commonly associated with ICI-associated neuropathies. When seen in relation to neuropathies associated with cytotoxic chemotherapy, adenocarcinoma was the most incident. In addition, hospitalization was more noticeable in patients with neuropathies associated with ICI, to carry out the treatment of adverse events they had. However, in these neuropathies, a better clinical response was also seen when ICI therapy was discontinued or corticosteroids were administered [3].

Although some severe peripheral neuropathies improve significantly with ICI discontinuation, it has been observed a long-term persistence of painful sensory neuropathy even without the medication [3]. In mild cases, there is no need for discontinuation of immune checkpoint inhibitor therapy or initiation of immune modulating treatment such as corticosteroids[8]. Besides the mild peripheral neuropathies, there have been described more widespread cases of inflammations such as meningoradiculitis or meningoradiculonevritis in patients treated with ICIs, mostly with Ipilimumab [11,14]. Recently studies showed that ICI induced peripheral neuropathies can focally or diffusely affect the sensory peripheral roots or motor or limb and can appear as axonal or demyelinating neuropathies [8,10]. Facial weakness and extraocular movement impairment may occur too [3].

Immune related neuropathies can occur after starting ICI therapy and can still be persistent and continue to be manifest even after stopping the immune therapy [15].

The variety of clinical forms involved in neuropathy associated with ICI deserves a review on its own. An interesting association is described by Alhammad *et al.* (2017): 2 rare cases of brachial plexus neuropathy were observed during treatment with ICI. The 2 cases started after the ninth monoclonal infusion and triggered sudden onset severe pain, in addition to paresis and paresthesia in the hand and upper limb, a clinical presentation compatible with neuralgic amyotrophy [16].

Finally, peripheral neuropathies may manifestate in very different ways raging from GBS to mononeuropathy of a single cranial nerve. While usually reversible, there are persistent cases that left long term sequelae. It is highly recommended Neuro-imaging and neurology involvement in this matter [17].

Guillain-Barré Syndrome and variants

GBS is a group of autoimmune disorders manifested by acute polyradiculoneuropathy, and it is the most common cause of acute flaccid paralysis [18]. It is estimated that 0.1 to 0.2% of patients receiving ICI develop acute demyelinating polyneuropathy which resembles GBS[7]. The disease presents in a progressive and symmetrical pattern with ascending sensory and motor dysfunction (paresthesia, muscle weakness, paralysis and sensory loss), autonomic neuropathy and areflexia [6,19–22]. Ultimately, GBS triggered by ICI is generally similar to GBS not associated with ICI in terms of presentation and clinical course [23]. Also similarly to GBS not associated with ICI, most cases can be classified as acute inflammatory demyelinating polyneuropathy (AIDP), although rare variants of the syndrome, such as Miller-Fisher syndrome, have also been reported. [24].

Another interesting information is that patients with melanoma may have a higher risk of ICI associated demyelinating polyneuropathy due to shared epitopes in both melanocytes and Schwann cells [25,26].

Corticosteroids are the first-line treatment for GBS caused by ICI [7], different from idiopathic GBS, in which corticosteroids treatment do not result in significant differences when compared to control groups [27]. This probably happens due to different etiopathogenesis involved in these two situations. Additionally, IVIG or plasmapheresis may be used in cases of poor clinical improvement [7].

Chronic Inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) may occur similarly to GBS in an acute manner in early stages, although can be distinguished by the response to corticosteroids therapy and the time course. The rapid begging of the symptoms suggesting AIDP has been described in a lot of cases that were finally diagnosed as CIDP induced by immune checkpoint inhibitors therapy following decompensation weeks after initial improvement [25,28]. CIDP is typically related to a slow disease course with time to at least eight weeks. Symptoms may continue progressing or it might occur in a relapsing-remitting course due to segmental demyelination and remyelination. Changes associated involving neurons may happen either. The mechanisms involved in this process are both humoral and cell mediated [26].

Myositis

Myositis are inflammatory myopathies that induce muscle inflammation associated that could have an extra muscular manifestation associated including cartilage, lung and skin manifestations [29]. Inflammatory myopathies can be classified into polymyositis, dermatomyositis, immune-mediated necrotizing myopathy (IMNM), sporadic inclusion-body myositis, and overlap myositis [29,30]. A Meta-analysis study by Psimara *et al.* (2018) reported the major complications in the peripheral nervous system during ICIs therapy. Among these complications myositis was the most commonly neurological AE of ICI reported. Patients who are treated with anti-PD-1 aAb like nivolumab have a 1% chance of being affected by ICI-induced myositis [31].

In the study by Moreira *et al.* (2019), of the 38 cases of patients

who had metastatic cancer and had neuromuscular AE due to therapy using ICI, 19 cases were reported to have myositis, which was the most common AE. Among the 38 cases, 22 were using pembrolizumab, 5 were nivolumab, 2 were ipilimumab and 9 were using combination. In addition, as the symptoms seen in the 38 patients with AE, proximal muscle weakness of the limbs and myalgia were the most frequently seen, with 12 and 16 cases, respectively. It was also analyzed for the presence of autoantibodies associated with myositis in 24 patients, with negative results in 67% of cases and an interesting fact found in this study is that 32% of these myositis patients had overlap myocarditis associated[32].

Also, the disease present high levels of creatinine kinase (CK) and EMG with myopathic pattern, and other less often symptoms as dyspnea, fever, fatigability, chest pain and dysphonia [33]. Other studies have reported that patients who developed myositis can also developed overlapping MG, and presented fluctuation weakness in ocular and bulbar muscles [34,35]

Cases of Myositis caused by nivolumab induced use to improve after drug withdrawal and administration of corticosteroid (usually prednisone or prednisolone) with or without immunosuppressive therapy [36]. Prednisone treatment consists in 0,5-1mg/kg, for patients unresponsive or partially responsive to corticosteroids it may be necessary plasmapheresis or high dose of endovenous immunoglobulin administration [34,37–39].

Myasthenia gravis

MG as a complication of ICI therapy, which can be seen as an aggravation of the syndrome already possessed or as a new case [25]. In a study citing nivolumab, the incidence of MG caused by an adverse effect of ICI therapy was 0.12%, occurring in 12 patients among 9,869 individuals with this therapy [40,41]. In the study of Sato *et al.* (2019), MG associated with ICI was 1.16% in 7,604 patients analyzed, when compared to the percentage of 0.03% without using ICI, in 383 patients analyzed [3]. Antibodies to the acetylcholine receptor (AChR) are identified in approximately 85% of patients with generalized myasthenia gravis and when myasthenia is considered an adverse effect of the use of ICI, positive results for the antibody are found in 66% of cases [42,43]. When AChR antibodies are detected, the results found are, in most cases, much lower when compared to those found in naive patients with ICI [44,45].

In a Japanese study conducted with nivolumab monotherapy in 9869 cancer patients, there were 12 cases of MG, which started in the initial phase of treatment and evolved rapidly. Markedly high CK levels were obtained in 10 of the 12 patients already diagnosed with MG, in which a mean serum CK of 4799 IU/L was obtained, being a high level that preceded clinical symptoms with MG related to nivolumab, which were also associated with worse prognosis [44]. In addition, it was also noted that of the 12 cases of MG associated with nivolumab, 10 patients were positive for AChR and that there were 4 cases of myositis, 3 cases of myocarditis and 1 had an association of the myositis and myocarditis, together with the presence of MG. Although these 2 complications mentioned are uncommon events, these disorders can develop simultaneously in patients with MG related to nivolumab [44]. Another study by Sato *et al*. shows the presence of overlap between myositis and MG in 20% of patients with MG associated with ICI [4].

In the study carried out by Suzuki S *et al*. (2017), which makes a comparison of the clinical characteristics between patients who have MG related to nivolumab and idiopathic MG. Dyspnea and limb muscle weakness in patients using ICI therapy were the most common presentations (67%). In idiopathic disease, diplopia (75%) and ptosis (85%) appear as the 2 most common symptoms caused [43,44]. Symptoms usually progress rapidly with frequent decompensation of the myasthenic crisis, which requires respiratory support. Almost all patients reported with MG related to ICI therapy required hospitalization, with 40-50% of these patients requiring mechanical ventilation. Which can be associated with patients with high CK levels, according to a study by Safa *et al.* (2019) [43]. In a retrospective cohort of 65 patients diagnosed with MG induced by ICI, the mean time from the onset of symptoms to respiratory failure and intubation was only 7 days [44]. This is notably distinct from myasthenia gravis not associated with ICI, which has as estimated risk of 15 to 20% over the life of myasthenic crisis, and in which just one fifth of patients have a myasthenic crisis at the time the diagnosis was made [46,47]. The evolution time from the onset of symptoms to the most severe symptoms in patients with MG related to ICI is from 1 to 60 days. On the other hand, in patients with idiopathic MG, the evolution time of the symptoms is approximately 2-3 years [42].

According to Suzuki *et al.* (2017), treatment using immunosuppressive therapy was effective in patients who had MG related to nivolumab, in which patients with mild symptoms responded to oral corticosteroids and the symptoms were relieved within weeks. However, more severe patients experienced a more delayed and gradual improvement, with 4 to 8 weeks [44]. Regarding the results of treatment and prognosis of the disease, in the study carried out by Safa *et al.* (2019), the symptoms of AE were completely resolved in 19% of patients, improved in 55% and worsened in 26%. 63% of the 38 patients who received first-line corticosteroid therapy improved their symptoms, while in the rest of the patients there was an evolution to respiratory failure. When IVIG or PLEX was used as the primary treatment, 95% of patients showed improvement in symptoms. In addition, death was reported in 37% of the patients, of which 23% were due possible complications from MG, after approximately 6 weeks after the initial MG symptoms, and the remaining deaths were due cancer progression, other comorbidities or were not identified [43].

Conclusion

Although uncommon, AE related to PNS feature several of serious complication, that can lead patients to a bad prognosis as hospitalization and even death. Moreover, with greater therapeutic use the AE are likely to increase incidence, becoming more important the better understanding of the mechanisms predisposing to development of neuropathy induced by ICI for formulating management strategies to avoid the development of this disease.

Author Contributions

I. **Conception and design:** all authors
II. **Administrative support:** all authors
III. **Provision of study materials or patients:** all authors
IV. **Collection and assembly of data:** all authors
V. **Data analysis and interpretation:** all authors

VI. **Manuscript writing:** all authors
VII. **Final approval of manuscript:** all authors

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Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare

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