Neuromuscular complications of immune checkpoint inhibitors

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■ Highlights

• Neurological irAE are very uncommon in cancer patients with ICIs treatment, in less than 3% of the patients, but with potentially poor outcome.
• ICI-associated myositis with or without myasthenia gravis are the more frequent complications and respond well to corticosteroid therapy and ICIs discontinuation.
• Oculobulbar involvement is unique and common among patients with ICI-associated myositis.
• Myocarditis is occasionally associated in irMyositis and consists with diaphragm disorder pejorative prognostic factors.

■ Summary

Immune checkpoint inhibitors have been increasingly used in patients with various cancers. Despite favourable oncological these treatments have also been associated with immune-related adverse events. Neurological irAE are rare but potentially severe and neuromuscular complications are the most common. This is a new group of neurologic complications of systemic anticancer therapies, often responsive to immune-modulating therapies. Early recognition and treatment are crucial for timely improvement of functional outcome and requires a multidisciplinary approach.

■ Introduction

The benefit of immune checkpoint inhibitors (ICIs) in oncology resulted in a paradigm shift in the treatment of many malignancies with immune agents target immune cells and not directly cancer
cells. By regulating T-cells pathways, ICIs enhance antitumor responses [1]. Since, pembrolizumab (an antibody targeting cytotoxic T lymphocyte associated antigen 4, CTLA4), has been approved in 2011 by the Food and Drug Administration (FDA) for advanced melanoma, other ICIs have also been approved for the treatment of various malignancies. Nivolumab and pembrolizumab, monoclonal antibodies directed against the programmed cell death 1 (PD-1) have been approved by the FDA in 2014, followed in 2016-2017 by the anti-PD-1 ligand (PD-L1) agents: Atezolizumab, Durvalumab and Avelumab. To date, more than a 1000 ongoing clinical trials investigate anti-PD1/PD-L1 drugs alone or in combination with other immunotherapies and/or other drugs.

Consequently, significant advances have been accomplished improving patients survival, but unfortunately increasing number of adverse events, hampering quality of life, have been associated with these treatments. These immune-related adverse events (irAEs), can involve any organ. The main irAEs concern gastrointestinal toxicities, skin disorders and endocrinopathies. Neurological irAEs (n-irAEs) are very rare, occurring in less than 3% of patients [2] but can be severe and potentially fatal requiring prompt recognition and treatment. Incidence of grades 3–4 irAEs are observed in less than 1% of patients [2–6]. In a recent retrospective study of all 4869 patients treated in Memorial Hospital between 2010-2017 [7], 81 patients developed n-irAE (1.6%). The risk appears higher in patients receiving combined anti-CTLA-4 and anti-PD-1 or others treatment. Of these 59% of patients (48 of 81) had a concurrent non-neurologic irAE.

This review will summarize the neuromuscular irAE of ICIs and will discuss their diagnosis and management with a final focus in patients with pre-existing autoimmune diseases.

**Major complications in the peripheral nervous system**

**Myositis**

Myositis is the most commonly reported ICI-associated (irMyositis) n-irAE. Patients often present with mild symptoms commonly with only myalgia. More severe presentations with pronounced inflammatory and/or necrotizing characteristics with symptoms mimicking myasthenia gravis [8] have also been reported. Differential diagnoses including ICI-induced myasthenia gravis (irMG), myositis associated with antisynthetase syndrome or paraneoplastic myopathies should be ruled out quickly. In irMyositis: (a) no extra-muscular clinical manifestation - e.g., cutaneous, interstitial lung disease- is observed; (b) all myositis-specific or associated antibodies-i.e. HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) and SRP (signal recognition particle) paraneoplastic antibodies- are negative. Muscle biopsy shows a specific pattern of inflammatory and necrotic changes (with locally clustering necrotic myofibers) in skeletal muscles [8]. To our knowledge, this pattern is quite specific and was never reported in well-known inflammatory myopathies.

At least 25 cases of irMyositis have been reported in patients with no pre-existing autoimmune disease (table I) [8-18]. Symptoms generally occur in the first two months of ICIs treatment with rapid progression. The clinical spectrum ranges from myalgia (16/21 of patients, 76%) to acute or subacute axial and limb-girdle distribution weakness (16/23 of patients, 69%), oculomotor weakness (12 patients, 48%) and bulbar involvement (10 patients, 40%). Ocular involvement, which is not typical seen in inflammatory or necrotizing autoimmune myopathies [19], occurs frequently in irMyositis and magnetic resonance imaging (MRI) shows abnormal T2 signal and contrast-enhancement of extraocular muscles consisting with ocular myositis [14]. Fluctuations or fatigability is an irMG cardinal feature but only rarely reported in these patients (2/25 patients). Myocarditis is reported in 35 % of the patients (8/23) and may support routine echocardiogram at the baseline. Clinicians should be vigilant for immune-mediated myocarditis, due to its early onset, non-specific symptomatology and fulminating progression [13]. Creatine Kinase (CK) levels are very high in serum samples with a median of 4565 (range 333-20270). Electromyography (EMG) show myopathic pattern. Good clinical and biological outcome after immunomodulatory treatment and ICI’s discontinuation is described in 21/25 of the patients (84%). Fatal outcomes have been described when associated with lesions in the myocardium or in the diaphragm [13,20,21]. In patients with irMyositis associated cardiac or diaphragmatic involvement, treatment escalation may be required beyond corticosteroids such as intravenous immunoglobulins, plasma exchanges, methotrexate or cyclophosphamide.

**Myasthenia gravis**

Immune-related myasthenia gravis (irMG) has been often described [22]. Diagnosis is based on clinical features and EMG demonstrating signs of neuromuscular transmission failure and/or the presence of serum anti-acetylcholine receptor (AChR) or antimuscle-specific kinase antibodies. A beneficial response to cholinesterase inhibitors is also supportive of this diagnosis. Of all reported patients only 8 were found with isolated irMG [23–30]. Several other reports of pre-existing myasthenia gravis (MG) exacerbated with ICIs [31-36] questioning the risk of treating patients with known MG (or other autoimmune disorders) with this agents (see chapter below). Patients with positive AChR antibodies in serum, without the clinical symptoms of MG, [37,38] are also at risk of developing the disease once treated with ICIs. It is worth noticing that, in pre-existing MG or isolated MG antibodies-positive patients, fatal outcomes were described [31,37]. In view of the clinical overlap with patients with myositis mimicking MG [8], it is possible that some of the patients reported in whom the diagnosis was based on the only clinical presentation (with
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Table I: Cases of immune checkpoint inhibitors-associated de novo Myositis (irMyositis)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Myalgia</th>
<th>Weakness</th>
<th>EMG results</th>
<th>Serum CK (n &lt; 200)</th>
<th>Myocarditis</th>
<th>Myopathy</th>
<th>irMyositis response to immune-modulating treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axial/</td>
<td>Oculo-motor</td>
<td>Bulbar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behling et al. [9]</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>NR 5148</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bourgeois-Vionnet et al. [10]</td>
<td>NR</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>MP 2450</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Diamantopoulos et al. [11]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>MP 4670</td>
<td>No</td>
<td>inconclusive</td>
</tr>
<tr>
<td>Fox et al. [12]</td>
<td>NR</td>
<td>NR</td>
<td>+</td>
<td>–</td>
<td>NR 1180</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Johnson et al. [13]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>NR 17750</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR 20270</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Liewluck et al. [14]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR 1284</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 2</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>NR 444</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>No 333</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shah et al. [15]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>MP 13710</td>
<td>Yes</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Case 2</td>
<td>NR</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>NR 924</td>
<td>No</td>
<td>ND</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>NR 2371</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Case 4</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR 514</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sheik Ali et al. [16]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR 1088</td>
<td>NR</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Touat et al. [8]</td>
<td>8/10</td>
<td>7/10</td>
<td>6/10</td>
<td>2/10</td>
<td>MP 2668</td>
<td>4/10</td>
<td>9/10</td>
</tr>
<tr>
<td>about 10 pts</td>
<td>9/10</td>
<td>10/10</td>
<td>(median)</td>
<td></td>
<td>10/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshioka et al. [18]</td>
<td>NR</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>NR 2812</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NR: not reported; Pts: patients; MP: myopathic; ND: not done.

Increased CK and negative EMG were misdiagnosed [6,15,39]. Interestingly, both disorders may co-occur in patients with confirmed MG and elevated CK as pathological evidence for myositis and/or myocarditis; [15,40-49] (Table II). Table II presented irMG with or without irMyositis in patients with no pre-existing autoimmune disease. Fatigability was seen in all patients (6/6). Anti-AChR antibodies are positives in 57% of patients (12/21) but none was seropositive for MuSK antibodies. EMG was conclusive in 50% of the patients (8/16). Good clinical outcome after immunomodulatory treatment and ICIs discontinuation is described in 90% of the patients (19/21). In a recent comparison of 12 patients with nivolumab-related MG (nivoMG), myositis and myocarditis and 105 patients with MG (MR group), it seems that the disease was more severe (with higher frequencies of myasthenic crisis and more rapidly deterioration) in the nivoMG patients [50]. Ten patients (83%) were positive for anti-AChR antibodies in the nivoMG group vs 78% for MG group. Serum CK levels were markedly elevated in the nivoMG patients to an average level of 4799 IU/L (normal = 200 IU/L) vs 119 IU/L for MG group (P = 0.003). No difference was seen in the frequencies of ocular, limb and neck muscle weakness. However, facial and bulbar signs are more frequent in nivoMG patients.

There is some unique characteristics in irMG. First, clinical onset occurs in the early phase after treatment initiation; the median time of myasthenic symptoms is 2 doses of ICIs (range 1-4). Second, the mean titer of anti-AChR antibodies is 8 times lower than seen in the idiopathic MG patients [50]. Third, myasthenic crisis or respiratory failure require ventilatory support in 42-50% of patients [22,50]; this is 7 times higher than in idiopathic MG. Fourth, response to corticosteroids (or other immunomodulatory treatments) associated to ICIs
discontinuation is in general good but partial; the general clinical irMG outcome can be poor mostly because of systemic issues. Frequent fatal outcome were described \[22\] mostly secondary to the oncological outcome, independently to n-irAE. Additionally, in patients with outcome, CK serum levels were often rapidly increasing; interestingly, nearly all reported fatal cases of irMG were associated with irMyositis \[29\]. Baseline serum CK and AChR-Ab should be part of the pre-ICI screening.

### Peripheral nerve disorders

Immune demyelinating polyradiculoneuropathy (irDP) is a common neuromuscular complication in ICI-treated patients. Unlike irMG or irMyositis, onset is more variable in irDP with presentation after median of 3.5 doses of ICIs. Acute or subacute presentation was reported with anti-PD1 and anti-CTLA4 treatment in 13 patients \[6,43,51–63\] with mainly solid cancer and exceptionally Hodgkin disease \(57\). Patients present with sensory-
motor symptoms and often cranial nerve involvement [43,51,53–56]. Importantly, cranial nerves palsies have been reported without an iDP [64,65]. Serum test and antigangliosides antibodies are classically absent. Cerebrospinal fluid (CSF) shows almost always evidence of albuminocytologic dissociation possibly associated with mild lymphocytosis (around 10–15 cells) [51–54] and a normal glucose level. EMG show evidence of demyelination with sural sparing pattern, prolonged F wave latencies and decrease motor conduction velocities and sometimes conduction block. Corticosteroids should be considered as the first-line treatment of choice. Even if corticosteroids are not usually indicated in the Guillain-Barre Syndrome, they have been associated with a favourable outcome in these patients [53,61]. IVig and occasionally plasma exchange should be associated in patients with severe clinical picture or who do not respond to corticosteroids. Chronic demyelinating polyradiculoneuropathy has been reported in only 4 patients [43,51,52,66], eventually following an initial acute presentation [66].

Diagnosis and management

The diagnosis of a peripheral nervous system n-irAE needs a careful strategy to rule out differential diagnosis, in particular tumour invasion. Formal neurological evaluation and a diagnostic workup, including serum studies, lumbar puncture, electro-neuromyography (ENMG) and eventually histopathological tests are required.

The management of irAEs are based on the grading of toxicity, according to common terminology criteria for adverse events (CTCAE). This evaluation requires close cooperation between oncologists and neurologists and should not delay discontinuation of the ICI treatment (for all CTCAE grades until the nature of the adverse event is defined) and the initiation of corticosteroids. The choice of immune-modulating treatment is guided by the severity of the neurologic toxicity. Corticosteroids should be considered as the first-line treatment of choice for all n-irAEs. For symptomatic grades 1–2 irAEs, corticosteroids (0.5–1 mg/kg/day of prednisolone equivalent) are recommended after withdrawal of ICI treatment. If recovery does not occur within 7 days, or for > 3 CTCAE grade, the patient requires immediate hospitalization and initiation of intravenous corticosteroid treatment and consideration of treatment escalation with plasma exchange, immunoglobulins, cyclophosphamide, rituximab, azathioprine or, methotrexate. These agents should be considered in patients who are unresponsive or only partially responsive to first-line therapy or in cases in which the sparing of corticosteroid agents is indicated [2]. As the half-life of ICIs is long (up to 2 months), corticosteroids may be tapered over a period of 2–3 months. Rechallenging may be possible but has to be discussed by organ specialist in multidisciplinary meeting.

Previous autoimmune disorders and ICIs

An important concern for physician is the use of ICIs in patients with history of autoimmune diseases (AID). Both, successful treatment and previous neurological disorder exacerbation have been described during anti-PD1 treatment [32,34,35]. In a retrospective series of 30 patients with AID who were treated with ipilimumab, 27% experienced exacerbation of their AID, and 33% had high-grade iAEs [67]. Three patients with previous neurological AID (one transverse myelitis and two multiple sclerosis) did not relapse on treatment but the patient with myelitis presented a different irAE (colitis). In a series of 52 patients with pre-existing AID, twenty patients (38%) had a flare-up of their symptoms (interestingly, none of the 5 patients with neurological disorders relapsed) requiring immunosuppression [68], but only 2 (4%) patients discontinued treatment. Other irAEs were reported in 15 (29%) patients, of which 4 (8%), discontinued treatment. Finally, in a recent retrospective series of 56 patients with pre-existing AID (active AID in 18% of the patients) undergoing PD-1 or PD-L1 inhibitor therapy for non-small-cell lung cancer, 13 patients (23%) developed an AID flare (risk increasing up to 50% if active AID), only 13% were grade 3 and 0% grade 4, and 21 patients (38%) an irAE (26% were grade 3 and 4) [69]. Management with corticosteroids has been required in 4 patients with exacerbation and 8 patients with irAE. Only 3 patients presented with neurological AID (MG: 1 and multiple sclerosis: 2) and none relapsed but 2 patients presented with new irAE (pneumonitis). Overall, findings from all series studies are similar with a risk to AID exacerbation around 30% but manageable toxicities even without necessity of discontinuing ICIs therapy. The identification of patients with autoimmune diseases, prior to treatment initiation, will allow specific follow-up during ICIs treatment. Patient education is essential; patients should be aware of the safety profile of the ICI they will receive and report any new irAEs. Although the toxicity may be somewhat higher, is manageable and patients can benefit from ICI treatment, most irAEs are low grade and reversible [68,69].

Conclusion

ICI-related neurological complications include a broad spectrum of syndromes involving the entire neuroaxis with peripheral nervous system seems predominantly susceptible. The risk of n-irAEs is rare when compared to all other irAEs of ICIs or to other standard treatments (e.g., chemotherapies) but severity can be very severe. Clinicians should be aware of these potential complications. The use of ICIs in patients with pre-existing autoimmune disorders, is higher, but is reported to be generally safe and treatable with predominantly CTCAE grade 1-2 toxicities. When n-irAE is suspected, prompt diagnosis can allow, discontinuation of the ICI and early treatment with corticosteroid. If the clinical outcome is poor within few days, clinician should
consider other immunotherapies; the choice is often centered specific and heavily influenced by clinicians and clinical experience. International guidelines on the management of these patients are required for standardized care for these difficult to treat patients.

References

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