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Case Report

Myasthenia Gravis and Myositis Overlap Syndrome Caused by Immune Check Point Inhibitor: A Case Report

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SUMMARY

Nivolumab, an immune check point inhibitor (ICI), inhibits programmed cell death protein 1 (PD-1) and increases the immunity to fight against the cancer cells. Myasthenia gravis (MG) is a rare and life-threatening adverse effect triggered by nivolumab. We described a 65-year-old patient with the hepatocellular carcinoma who developed MG and myositis after one cycle of nivolumab. The myasthenic symptoms deteriorated to impending myasthenic crisis in few days despite high dose steroids. We performed plasmapheresis and reversed the progressions to respiratory failure. Early recognition and comprehensive investigation of MG is important in these patients with ICI therapy. Concurrent treatments of plasmapheresis and steroids for ICI-related MG may be an effective management.

1. Introduction

The use of immune check point inhibitors (ICI) is a novel therapy for patients with advanced cancers. As the expanding experience of these ICI in various cancers, there has been increasing recognition of ICI-related adverse events (irAEs).[1] Among these irAEs, an overlap syndrome, which is comprised of myasthenia gravis (MG), myositis and myocarditis, has been reported. Not only that the ICI-related myocarditis has a high mortality rate, the ICI-related MG also has unique features and carries a poorer prognosis compared to the classic MG.[2] The early recognition of this overlap syndrome and the initiation of relevant treatment as early as possible may improve the outcomes.

Nivolumab, one of the ICIs, is a monoclonal antibody against programmed death-1 (PD1) to enhance the antitumor immune response. However, this effect will break immune tolerance to self-antigens and lead to dysimmune-mediated toxicities.[1] Here, we present a patient with hepatocellular carcinoma who had soon developed an ICI-related overlap syndrome with generalized MG and myositis after treated with just one standard dose of nivolumab. This patient responded remarkably with early concomitant use of steroid and plasmapheresis.

2. Case report

A 62-year-old man with history of chronic obstructive pulmonary disease and hepatocellular carcinoma AJCC stage 2 received an ICI therapy. The regimen was nivolumab at dose of 2 mg/kg (total 140 mg). One week later, he had left ptosis without obvious diurnal fluctuation. Weakness in the neck and four limbs, shortness of breath and myalgia were noted in the following days. On assessment, there were ptosis and weakness in proximal four limbs, neck and trunk. The Medical Research Council grading of muscle strength was four in proximal upper and lower limbs, five in distal limbs and three in neck and trunk. The deep tendon reflexes and sensation were normal. Biochemical blood tests reported creatinine phosphokinase (CPK) 6262 U/l (normal: < 250 U/l)), ALT 275 U/l (normal: < 44 U/L), and AST 492 U/l (normal: < 38 U/L). Acetylcholine receptor antibody (AchR) was 10.63 nmole/L (normal: < 0.2 nmole/L). There were no remarkable findings of electrolytes, thyroid function studies and cardiac enzymes. The autoimmune surveys, including antinuclear antibody, anti-ENA screen, anti JO-1 and Anti-ds DNA, were within normal ranges. The lung function test showed restrictive lung volumes. Nerve conduction studies, including distal latencies, motor and sensory amplitudes and conduction velocities, were normal. High-rate and low-rate repetitive nerve stimulation (RNS) tests showed no decremental response in trapezius and nasalis. However, the stimulation single-fiber electromyography (EMG) showed abnormal jitter with the mean of mean consecutive difference at 35 μs (normal range < 20 μs) in the orbicularis oculi. The concentric needle EMG study demonstrated diffuse fibrillation potentials and typical short-duration, low-amplitude polyphasic motor unit action potentials with early recruitment pattern in the biceps and quadriceps. Based on above findings, this patient was diagnosed as having MG with myositis after nivolumab therapy.

Initially, we started prednisolone at the dose of 60 mg/day and pyridostigmine 60 mg 4 times daily. Five days later, the CPK level decreased from 6262 U/L to 838 U/L. Nevertheless, the muscle strength continued to deteriorate resulting dyspnea despite oxygen supply. Noninvasive bilevel positive pressure ventilation (BiPAP) was used for the respiratory distress with CO2 retention. Plasmapheresis

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was performed as a rescue therapy of myasthenic crisis. After four sessions of plasmaphereses, BiPAP support was discontinued gradually. Weakness in proximal limbs and neck improved after whole course of plasmapheresis (Figure 1). One month later, the patient recovered to independent status and prednisolone was reduced to 30 mg daily.

3. Discussion

We describe a case of ICI-related overlap syndrome after nivolumab therapy. The diagnosis of MG was confirmed by abnormal single-fiber EMG and elevated AchR antibody titer, and myositis was supported by elevated serum CPK level. Although myasthenic crisis developed in a few days, he was treated successfully with early concurrent use of steroids and plasmapheresis.

Myasthenia gravis (MG) is an autoantibody-mediated neuromuscular disorder potentially triggered by immune checkpoint inhibitors (ICIs). To date, several immune checkpoint blockade therapies, including anti-PD-1 and its ligand, and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) therapy, have been identified to be associated with MG. Most cases of ICI-related MG were treated with anti-PD-1 (Nivolumab and Pembrolizumab). Programmed death-ligand inhibitors (Durvalumab) and anti-CTLA-4 (Ipilimumab and Tremelimumab) related MG have also been reported.[3] Previous literatures have shown similar clinical features of MG associated with Ipilimumab or Pembrolizumab to Nivolumab-induced MG.[2]

ICI related MG is a rare and severe irAEs. Among 9,869 patients with cancer treated with nivolumab, only 12 MG cases (0.12%) were identified. Four of these patients also had myositis.[2] The clinical features of ICI-related MG are different from the classical MG. The patients with ICI-related MG are older at the onset and have more aggressive and severe course than classic MG. The ICI-related MG usually occurs in the early phase of administration of ICI, which more than half of the patients develop MG after one or two cycles of ICI.[2] Almost half of the patients with ICI-related MG have respiratory failure requiring mechanical supports. Furthermore, other complications, such as myositis, myocarditis and polyneuropathy, could also be detected in the patients with ICI-related MG.[4]

Apart from the above clinical manifestations, the ICI-related MG has a lower positive rate of AChR antibody and electrodiagnostic studies than classical MG.[4,5] The lower positive rate of electrodiagnostic and serological studies makes it more difficult to identify ICI-related MG earlier. Our case has the similar findings of electrodiagnosis studies with no typical decremental responses in RNS despite dyspnea and severe muscle weakness. Therefore, single-fiber EMG study and serum AchR antibody are helpful in the diagnosis of ICI-related MG.

Current therapies for classic MG include intravenous immunoglobulin (IVIg), plasmapheresis, steroids, and immunosuppressants such as azathioprine and rituximab. On the contrary, the first-line management of ICI-related MG is discontinuing ICI and early initiation of steroids. Plasmapheresis, IVIg and immunosuppressants are recommended in the patient refractory to steroids.[6] However, early initiation of IVIg or plasmapheresis are shown to have better clinical prognosis than those with steroids alone (95% vs. 63% improvement of MG symptoms).[3] Therefore, early use of plasmapheresis or IVIg in combination with high-dose steroids might be required in ICI-related MG.[7]

There are several reasons for the preference of early treatment with IVIg or plasmapheresis in ICI-related MG. First, the patients of ICI-related MG have high severity of Myasthenia Gravis Foundation of America (MGFA) clinical classification and rapid progression, which the median time of deterioration from the MG symptom onset to MGFA class IV/V is seven days.[3] Using steroids alone, which often takes several weeks to reach immunomodulation effects, cannot decelerate progression in time. On the other hand, plasmapheresis and IVIg are fast-acting treatments which come into effects within seven days.[8] Second, 25–75% of the patients with high dose steroids might experience transient worsening of MG symptoms and sometimes lead to respiratory failure,[9] and plasmapheresis and IVIg can reduce the risk of these exacerbations. Third, unlike classic MG, the ICI-related MG usually occurs with myositis and myocarditis and involves more other different organs.[10] Those who coexist with myositis and myocarditis have more severe clinical conditions and higher mortality.[3] Detailed investigations of peripheral nervous systems, heart and respiratory condition are necessary for the therapeutic strategy for the patients with ICI-related MG. As identification with overlapping syndrome, early treatment with plasmapheresis or IVIg

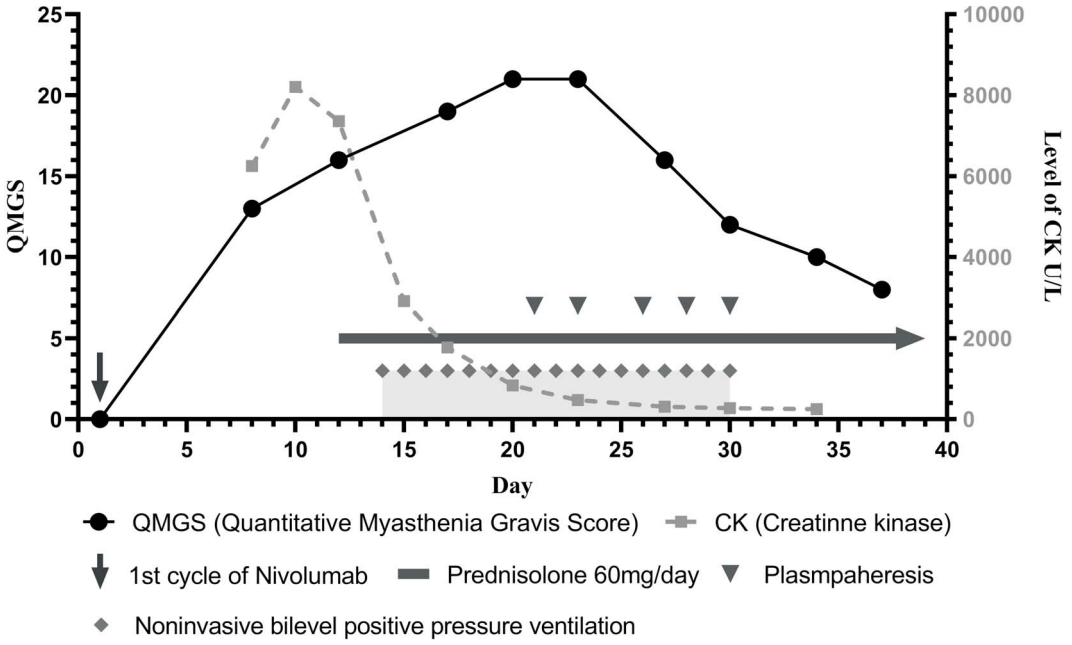

Figure 1. Schematic representation of clinical courses and treatment

should be more suitable rather than steroids alone regardless of the severities of initial symptoms.

In Taiwan, only four patients of ICI-related MG have been reported.[11–14] All patients were treated with steroids. Two died of myasthenic crisis and complications using steroids. None of these cases was treated with plasmapheresis. Early plasmapheresis halts the clinical deterioration and prevents the respiratory failure needing intubation, suggesting that early combination of plasmapheresis and steroids could effectively eliminate the neural autoantibody and pro-inflammatory cytokine complement. In our case, the myasthenic symptoms progressed to myasthenic crisis in just four days after steroids despite resolution of CPK level and myalgia. Rescue therapy with plasmapheresis resolved both conditions. As the appliance of ICI for different kinds of cancers have expanding, the numbers of patients caused by ICI-related adverse effects might increase continuously in the future. Early recognition and early combination therapy of steroids and plasmapheresis might be effective therapeutic strategies in the patients with ICI-related overlap syndrome with MG and myositis.

Conflict of interest

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