Review Article

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Immunotherapy Related Myasthenia Gravis and Lambert Eaton Syndrome Case Reports and Review of Literature

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Abstract

Neurological complications associated with immunotherapy are rare but potentially life threatening. Myasthenia Gravis (MG) and Lambert Eaton Syndrome (LEMS) are both rare neurological disorders. Here we present a case report of immunotherapy associated Myasthenia Gravis (irMG) and another one with immunotherapy associated LEMS. Less than 50 cases of irMG have been reported worldwide. IrMG happens early in the course of immunotherapy with a median of 6 weeks. About one third of the patients with irMG have immunotherapy related myositis or myocarditis. It is important to check Creatinine Phosphokinase (CPK) and troponin in all patients diagnosed with irMG. There is a 30.4% MG-specific mortality associated with irMG.

LEMS is a very rare disorder with annual incidence of one-tenth to one-fourteenth of MG. Only 2 cases of immunotherapy related LEMS have been reported so far. Here we report the first patient with immunotherapy related LEMS (irLEMS) associated with Atezolizumab. irLEMS happens later in the course of immunotherapy after 4 months of treatment.

Introduction

The use of immune check point inhibitors (programmed cell death protein 1 (PD-1) and PD ligand 1 (PD-L1)) and Cytotoxic T- lymphocyte associated protein 4 (CTLA-4) inhibitors has been expanding rapidly and many patients with metastatic cancer are living longer. Immunotherapy is generally well-tolerated but serious complications can happen.

About 60-78% of patients treated with PD-1 and PDL-1 antibodies experience side effects [3]. Common side effects include the following: fatigue in 16-24% of patients treated, rash in 30-40% of patients, and hypothyroidism 4%-12% [1-3].

Grade 3 toxicities have been reported in 6%-12% of patients including pneumonitis, colitis and hepatitis [3].

Within the 59 clinical trials (totaling 9208 patients) analyzed, the overall incidence of Neurological Adverse Esvents (NAE) was 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with the combination of both [3]. The clinical spectrum of neurological disorders was highly heterogeneous. Most of these nAEs were grade 1-2 and consisted of non-specific symptoms such as headache (55%) [4]. The incidence of high grade nAEs was less than 1% [4].

Reported high grade nAEs include immune mediated polyneuropathies, Guillain-Barré syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome, aseptic meningitis, transverse myelitis and immune encephalitis [4,5].

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A large retrospective study from Japan analyzed data from 2014 to 2016 of 9,869 patients treated with nivolumab, and 408 patients with ipilimumab [6]. This study reported that immunotherapy related myasthenia gravis (irMG) is a rare complication of immunotherapy. Incidence is about 1 in 1000 patients treated. Fewer than 50 patients with irMG have been reported worldwide [6,7].

In one review of 23 reported cases of irMG, 72.7% were *de novo* presentations, 18.2% were exacerbations of pre-existing MG and 9.1% were exacerbations of subclinical MG [7]. About 40% of patients with irMG had associated myositis and 30% with myocarditis and 10% with both [6,8]. Idiopathic MG is rarely associated with myositis. Bulbar symptoms and myasthenic crisis were observed more frequently in irMG than idiopathic MG [6,9]. There is a 30.4% MG-specific mortality associated with irMG [7].

IrMG has been reported with pembrolizumab [7] nivolumab, [9] and avelumab [10]. IrMG has also been reported with CTLA-4 inhibitor ipilimumab in combination with PD1/PDL1 inhibitors [9,11]. Single agent ipilimumab is not associated with irMG [6].

Patients and Methods

First Case report- Immunotherapy related Myasthenia Gravis

A 76-year-old Caucasian male presented with adeno-squamous carcinoma of lung with metastasis to bilateral scapulae with severe impairment of bilateral upper extremity function.

The carcinoma was PDL-1 positive with TPS (tumor proportion score) of 50%. Next generation sequencing was positive for PIK3CA mutation. No other mutations were detected.

The patient received palliative radiation 3000 cGy in 10 fractions to the bilateral upper extremities. Systemic therapy was started with pembrolizumab 200 mg fixed dose IV every 3 weeks two days after completing radiation. The patient was hospitalized within a few days after the second dose.

The patient's initial symptoms were blurred vison and ptosis, muscle weakness as well as shortness of breath. Lumbar puncture with cerebrospinal fluid analysis was unrevealing. MRI brain was negative.

The patient was found to be Ach receptor antibody positive and creatinine kinase was elevated at 1600.

He was promptly treated with steroids, IVIG and pyridostigmine. Patient had a complete recovery after 3 months of treatment. He died due to disease progression.

Second Case Report -Immunotherapy related Lambert-Easton Myasthenia Syndrome (LEMS)

A 65-year-old Caucasian Female diagnosed with Metastatic small cell lung cancer with left lung mass, mediastinal adenopathy and right liver metastases in November of 2018.

She received 4 cycles of carboplatin, Etoposide with Atezolizumab 4 cycles per guideline. This was followed by Atezolizumab maintenance 1200mg IV every 3 weeks from 02/18/2019 to 10/23/2019. Treatment stopped after patient was hospitalized with muscle weakness. She presented with progressive proximal muscle weakness with inability to walk. She had dysarthria. No ptosis or extraocular muscle weakness. No difficulty in breathing.

Work up showed elevated Voltage Gated Calcium Channel (VGCC) Antibody of>405. Acetyl choline receptor antibodies were negative at 0 and Anti-Musk antibodies were negative with at 0. CT scans of chest abdomen and pelvis at that time and 3 months later showed no evidence of small cell carcinoma progression. The lung and liver lesion continue to shrink. MRI brain with and without contrast remain negative for metastasis.

She received IVIG (2g/Kg for 5 days followed by 1g/kg monthly). Started on prednisone 20 mg three times a day initially. She could not be tapered off steroids and maintained on prednisone as above. She was started on Amifampridine [12] with dose escalation to 60g/day. She was wheelchair bound and able to walk short distances with walker. She continued to have speech difficulty.

Discussion

Myasthenia Gravis

Myasthenia gravis is a rare but life-threatening neurological complication of immune check point inhibitors and CTLA-4 inhibitors. Prevalence is roughly 1 in 1000. With more patients receiving immunotherapy, the absolute number of patients who develop MG will rise.

High clinical suspicion is important as this usually happens after the first or second dose of immunotherapy with a median time of 6 weeks [6,7]. Usual clinical findings are diplopia or ptosis nd dysphagia. Muscle weakness and respiratory failure may follow soon. These symptoms may mimic brain metastasis or cerebrovascular accident.

Immune-related myocarditis has a higher prevalence of 0.6 to 1.3% [13] and also happens early with a median of 6 weeks after immunotherapy.

In *de novo* MG about 85% tested positive for Ach Receptor antibodies. With immune-mediated MG 50-70% of patients [6] tested positive for Ach receptor antibodies.

We recommend cessation of immunotherapy immediately if patient develops any new neurological symptoms early in the course of immunotherapy. If MRI brain is negative, then testing for Ach Receptor antibody, creatine kinase and troponin level is recommended. In patients with bulbar symptoms with negative acetylcholine receptor antibody, need to be tested for Muscle Specific Kinase (MuSK) antibodies.

Treatment for immune-mediated MG is similar to idiopathic MG patients with high-dose steroids, intravenous immunoglobulin, plasmapheresis and pyridostigmine. In one case report from Canada, a patient with pembrolizumab-associated MG and myositis with myocarditis was refractory to steroids. One dose of 30 mg alemtuzumab was associated with favorable outcome [14].

Weiner *et al.* have successfully treated a patient with Nivolumab after low grade irMG symptoms have resolved [11]. We recommend against resuming immunotherapy for severe irMG (patients requiring hospitalization and presenting with respiratory distress) until further data is available.

Eaton-Lambert Myasthenia Syndrome

The estimated worldwide prevalence of LEMS is about 2.8 per million [15], making it a very rare disease. There are approximately 400 known cases of LEMS in the United States.

Lambert-Eaton myasthenic syndrome is an autoimmune disorder [16] of reduced acetylcholine release from the presynaptic nerve terminals due to antibodies to voltage-gated calcium channels in the presynaptic neuronal cell membrane.

The release of ACh is dependent on the influx of calcium ions via the Voltage-Gated Calcium Channel (VGCC). In Lambert-Eaton myasthenic syndrome, VGCC is reduced due to the IgG antibody-mediated cross-linking of the channels.

In 60% of patients with Lambert-Eaton myasthenic syndrome the disease is associated with SCLC [15]. The tumor tissue expresses VGCC. Autoantibodies created against the VGCC cross react with presynaptic VGCC antigens [17].

Non-tumor Lambert-Eaton myasthenic syndrome is associated with HLA-B8 (HLA - class I) and HLA -DR3 and -DQ2 (HLA class II) [17].

The most frequent clinical manifestations of Lambert-Eaton myasthenic syndrome are proximal muscle weakness, autonomic dysfunction, and absent deep tendon reflexes and dysarthria [15]. Ptosis and diplopia can happen. Autonomic dysfunction is reported in 80 % or more of the patients [18]. Post exercise facilitation can happen in EMS unlike Myasthenia Gravis.

PubMed search revealed only 2 reported cases of immunotherapy related Lambert-Eaton myasthenia syndrome. The first case report was from Japan in a patient with squamous cell lung cancer after receiving 20 weeks of Nivolumab [19]. The second case report was from USA in a patient with Small Cell Lung Cancer after receiving 4 months of combination immunotherapy with ipilimumab and Nivolumab [20].

In contrast to irMG which happens early in the course of immunotherapy, immunotherapy related LEMS happens after several months of therapy.

LEMS is a chronic condition. In a long-term study of 47 patients

with Non-tumor Lambert-Eaton myasthenic syndrome, 10 patients died at a mean age of 70 years and after a median symptom duration of 11 years [21].

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