A severe case of Pembrolizumab-induced triad of myasthenic crisis, myocarditis, and anti-SSA myositis

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Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by fatigable weakness involving ocular, bulbar, respiratory, and/or limb muscles. The weakness is due to an antibody-mediated immunologic attack directed at acetylcholine receptors or receptor-associated proteins in the postsynaptic neuromuscular junction.

Immune-related myasthenia gravis (irMG) is one of the rare but life-threatening immune-related adverse events (irAE) described with the use of immune checkpoint inhibitors (ICI). There appears to be an intimate link between autoimmunity and anti-tumor effect elicited by immune checkpoint inhibitors such as pembrolizumab. Onset of immune-related adverse events appears to be more strongly associated with anti-PD-1 (like pembrolizumab) and anti-PD-L1 antibody response than to other types of ICI. As such, reports of immune-related adverse events including potentially devastating side effects and their management are important.

We report a case of a man in his late 70s who presented with one week of progressive chest and muscle pain, generalized weakness, and fatigue. He received a single infusion of pembrolizumab three weeks prior as adjuvant immunotherapy for stage IIb malignant melanoma after undergoing wide local surgical excision. He was started on steroids for pembrolizumab-induced myositis and myocarditis. Symptoms progressed to include severe dyspnea, dysphagia and eyelid ptosis requiring tracheostomy and PEG tube placement. Serologic studies ultimately confirmed myasthenia gravis and anti-SSA myositis.

He was emergently treated with plasma exchange, pyridostigmine, Intravenous Immunoglobulin (IVIG) and is making gradual improvement with physical therapy and oral prednisone taper.

This case study presents a severe case of Pembrolizumab-induced triad of myasthenic crisis, myocarditis with myositis specific anti-SSA 52kD Ab IgG autoantibody for the first time. More studies are needed to assess the clinical significance and prognostic value of this autoantibody in patients presenting with Pembrolizumab-induced triad.

Case Presentation

This is a case of a man in his late 70s with hypertension and COVID-19 four months prior from which he recovered without residual respiratory symptoms. He is a nonsmoker who exercises regularly, doing home yoga and going to the gym three times a week.

He was diagnosed with malignant melanoma of his left lateral neck and underwent wide lateral surgical excision of a T4a, pN0, cM0 lesion, which was stage IIb on pathologic staging with negative sentinel lymph nodes. Adjuvant immunotherapy was recommended, and he received a single infusion of pembrolizumab. Two weeks later, he presented with cough, generalized body aches, fatigue and profuse sweating. The following day, he reported chest pain, generalized muscle pain, shortness of breath, hot flashes, nausea, vomiting, extreme fatigue, and poor appetite. In the emergency room, he was noted to be afebrile with hypertension, tachycardia and tachypnea. Labs were notable for elevated troponin (3881), liver enzymes (ALT 338 U/L, AST 439 U/L), and creatine kinase (4142 U/L). He was admitted to the hospital and started on intravenous fluids and heparin drip for the troponin elevation. Overnight, he developed dyspnea on exertion and labored breathing with worsening chest pain. EKG revealed sinus rhythm with right bundle branch block. Coronary angiogram identified two-vessel nonobstructive stenosis for which medical management was recommended. He was started on prednisone 100 mg daily due to concern for pembrolizumab-induced myositis and myocarditis. Transaminases and CK were improving on prednisone. On hospital day 4, he had progressive and persistent dyspnea with associated hypoxia, tachypnea and accessory respiratory muscle use, increased supplemental oxygen requirement, dysphagia and bilateral ptosis. Respiratory vitals revealed negative inspiratory force (NIF) -25 with vital capacity (VC) 1000 mL. He was transferred to ICU and placed on bilevel positive airway pressure (BiPap) ventilator. Emergent plasma exchange was initiated for suspected myasthenic crisis, and he was started on pyridostigmine and switched to IV methylprednisolone. He developed neck extensor muscle weakness and hypophonia before making gradual improvement in NIF and VC. After the 4th plasma exchange, NIFs were consistently -40. Dyspnea and dysphagia was subjectively improving and he was off BiPap, on 2-3 liters of nasal cannula supplemental oxygen. Walking distance was increasing with physical therapy, but he developed acute worsening of dyspnea with lethargy, NIF of -20, VC 1100 mL, respiratory acidosis with hypoxemia on arterial blood gas, worsening leukocytosis (WBC 37.02), acute kidney injury, and decreased urine

output. Pressors and broad-spectrum antibiotics were started due to concern for sepsis secondary to pneumonia. BiPap was resumed and the 5th plasma exchange was completed.

With worsening respiratory function (NIF -15, VC 750 mL), he was treated with IVIG (1 gram /kg daily) for 2 days with gradual improvement in NIF to -40. BiPap was discontinued but he subsequently developed worsening leukocytosis, elevated lactate and procalcitonin. CT chest revealed worsening bilateral lower lobe consolidations, concerning for mucus plugging. He required intubation for worsening hypoxia. Hypothermia and hypotension were noted, requiring broader spectrum antibiotic coverage for septic shock and vasopressors for hemodynamic support. Continuous renal replacement therapy (CRRT) was initiated for renal failure. Once renal function was recovering, a second round of plasma exchange was initiated but terminated after 3 exchanges due to thrombocytopenia and anemia requiring transfusion. Ultimately, percutaneous endoscopic gastrostomy (PEG) tube and tracheostomy were placed. Patient was discharged in a stable condition to a long-term acute care facility on hospital day 37.

Investigations

As part of his oncology workup for his malignant melanoma, he underwent whole-body PET scan. No focal metastatic disease identified. MRI head with and without contrast revealed no intracranial metastatic disease.

During admission, troponin peaked at 7359. EKG for chest pain revealed sinus rhythm with premature atrial complexes and right bundle branch block. Subsequent coronary angiography was nonischemic, revealing a normal left main trunk, 50% stenosis of the mid LAD with 30% stenosis distally, normal circumflex artery and mild atherosclerosis of the RCA. Echocardiogram revealed normal biventricular size, ejection fraction 65%, no regional wall motion or valvular abnormalities. CT angiography of the chest revealed no aortic dissection or pulmonary embolism.

Serologic studies revealed positive acetylcholine binding antibody at 2.84 (reference range 0.00-0.24), positive acetylcholine modulating antibody at 58% (reference range 0-45%) and negative MuSK antibody. Myositis panel revealed an elevated anti-SS-A 52kD antibody IgG of 31 (reference range <20) and negative antibodies for Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, TIF-1gamma, MDA-5 (CADM-140), NXP-2 (P140), PM/Scl-100, Ku, U1 RNP, U2 RNP and U3RNP (Fibrillarin). Serum paraneoplastic antibodies were negative. No thymoma on CT chest. Electromyography was not available during hospital admission. Creatinine kinase was elevated at 4142 on admission, which normalized prior to discharge.

Fluctuating leukocytosis with recurrent concerns for sepsis with white blood cell count 14.25 on admission, peaking at 37.02, normal at discharge. Platelets were normal at 279 on admission and as low as 33 after the development of thrombocytopenia with plasmapheresis, improving to upper 60s at time of discharge.

Treatment

He was started on prednisone 100 mg (1 mg/kg) daily due to concern for ICI-related myositis and myocarditis. After the development of ptosis, dysphagia and deterioration of respiratory status, he was started on pyridostigmine 60 mg three times daily and emergent plasma exchange was initiated for presumed ICI-related myasthenia gravis. With worsening dysphagia, prednisone was transitioned to IV methylprednisolone. Five plasma exchanges were completed with some recovery of respiratory muscle strength and ability to come off BiPap support. This improvement was followed swiftly by the development of pneumonia with septic shock and subsequent worsening of respiratory function. He received 2 days of IVIG 1 gram/kg/day and respiratory muscle weakness again improved followed by acute respiratory acidosis with hypoxemia, requiring intubation and tracheostomy. He required supportive treatments with broad-spectrum antibiotics, vasopressors, and CRRT. A second round of plasma exchange was initiated, and he underwent 3 exchanges before developing significant anemia and thrombocytopenia requiring transfusion. He remained on methylprednisolone 40 mg IV and pyridostigmine 90 mg four times daily on discharge to long-term acute care facility. Shortly after transition to long-term facility, methylprednisolone was changed to prednisone 30 mg daily. He is currently on prednisone 10 mg daily.

Outcome and Follow-up

Patient was discharged to long-term acute care facility after a 37-day admission. At the time of his discharge, he had tracheostomy and PEG tube placement. His anemia, thrombocytopenia and renal functions were improving. Troponin and creatine kinase elevations had normalized. After 7 weeks in rehab, he was discharged home with home health. He was seen in follow up in the neuromuscular clinic and is doing very well with oral prednisone taper.

Discussion

The use of immune checkpoint inhibitors as standard of care and as an adjuvant immunotherapy has been a major breakthrough in several types of malignancy, and its use is expected to expand. Neurological complications and life-threatening immune-related adverse events (irAEs) including immune-related myasthenia gravis (irMG) and immune-related myositis are very well described and can limit their clinical use.[1-3]

Pembrolizumab is one of the immune checkpoint inhibitors which can be used as adjuvant immunotherapy in some forms of malignancy. Mechanism of action includes interference of binding of PD-L1, the ligand for

the programmed death 1 protein to PD-1 on T-cells. This normally blocks T-cell activated destruction of the cell, and by blocking this process PD-1 and PD-L1 inhibitors permit T-cell mediated destruction of malignant cells. This process can cause a range of irAEs, however.[4]

The neurological autoimmune side effects can be mild to life threatening in some cases. The central and the peripheral nervous system can be affected, and side effects include seizures, encephalitis, leukoencephalopathy, myelopathy, polyneuropathy, MG and myositis.[1] In many reported cases of irMG, patients were older males who presented with myasthenia gravis, myositis and/or ptosis that followed soon (about a month) after they received pembrolizumab. They can have severe clinical presentations, rapid clinical deterioration with long-term sequela and high mortality rates.[5] Some patients present with a triad of MG, myositis and myocarditis and seem to develop respiratory failure more frequently than those with MG alone. Most of the death from MG complications was seen in those with elevated CK levels with MG overlapping with myositis and myocarditis. Patients with elevated CK seemed to develop respiratory failure more than those with normal levels. Overall, patients who were tested for CK and/or troponin seemed to have a higher MG deterioration rate and a higher mortality rate primarily because of MG complications. Patients with irMG who present with more than one organ involvement such as myositis, myocarditis, pneumonitis, hepatitis, and peripheral neuropathy have higher mortality.[6,7]

Our patient presented with the clinical triad of myositis and myocarditis followed by severe life-threatening bulbar myasthenia gravis requiring intubation, tracheostomy, and PEG placement. He developed his symptoms 2 weeks after his first dose of pembrolizumab and was found to be positive for acetylcholine-binding antibody, acetylcholine-modulating antibody and anti-SSA 52kD antibody.

Anti-acetylcholine receptor antibodies were the most commonly found antibodies followed by anti-MuSK and anti-striated muscle antibodies in patients with overlapping MG, myocarditis and myositis.[5] However, no cases have been reported regarding the type of myositis antibodies seen in pembrolizumab-induced myositis or the triad of MG, myositis, and myocarditis. We report positive anti-SSA antibody for the first time in a patient with this triad. Anti-Ro/SSA antibody, mostly directed against the Ro52 subunit, is the most prevalent myositis-associated antibody and is found in more than 30% of patients with myositis.[8] A systematic review in 2019 reported poor prognosis in MG combined with hyperCKemia with immune checkpoint inhibitors but no myositis antibody panel was performed.[9] In most of cases with ICI-related myositis, myositis-specific (MSAs) or myositis-associated (MAAs) antibodies were undetected.[10]

The use of low-dose steroids can prove to be effective for patients with irMG.[11] Early use of IVIG and PLEX have led to favorable outcomes in most patients with severe iMG, and their early use is recommended preceding or simultaneously with steroids to overcome the risk of a transient worsening, especially in patients with severe disease.[6,7,12]

Based on American Society of Clinical Oncology (ASCO) guidelines our patient meets definition of grade 4 myasthenia gravis (MG-G4) and given the significant risk of mortality associated with MG- G4, it is recommended that immune checkpoint inhibitors be discontinued permanently.[13]

Permanent discontinuation of therapy should also be considered in grade 2 or greater myocarditis (with abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay defining grade 2 myocarditis) and grade 4 myositis (severe weakness limiting self-care activities of daily living). There have been a few studies evaluating recurrence of ICI-related irAEs after rechallenging of ICI therapy. Recurrence of irAEs seem to vary from 28.8% to around 60% after rechallenging.[14-18]

Oncologists, Neurologists and Internists should have a high index of suspicion to recognize the neurological complications of immune checkpoint inhibitors, discontinue the medication as soon as possible and start aggressive immunosuppressive modalities to reduce mortality.

Learning Points/Take Home Messages

- With increasing applications for immune checkpoint inhibitors, their use is expected to increase. It is important for patients to be educated regarding the risks, benefits, and potential severe side effects related to these therapies, including the potential for developing myasthenic crisis, myocarditis and myositis.
- ICI-related myasthenia gravis overlapping with myositis/myocarditis has more severe symptoms, worse clinical outcomes and higher mortality than patients with MG alone and requires aggressive management with IVIG or PLEX as first line regimen in addition to steroids.
- Further studies are needed to assess if anti-Ro52 antibody could have a prognostic value for higher risk of respiratory failure in patients presenting with the triad of MG, myocarditis and myositis

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