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Case-based Review

Autoimmune myositis and myasthenia gravis resulting from a combination therapy with nivolumab and ipilimumab for metastatic melanoma

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Abstract

Checkpoint inhibitors are a novel option in the management of metastatic melanomas and many other malignancies. They are used to promote the activation of cytotoxic T-lymphocytes by inhibiting deactivation signals, enabling the immune response to the tumor. Numerous Immune-related adverse effects caused by checkpoint inhibitors have been reported in the literature. They are diverse in nature, and many are life threatening. We report a case of autoimmune myositis and myasthenia gravis following treatment with a combination of ipilimumab and nivolumab for metastatic melanoma.

Keywords: Checkpoint inhibitors, myasthenia gravis, myositis

Introduction

It has been recognized that tumors exert a level of immune tolerance by creating an immunosuppressive milieu (1). Therefore, new approaches have been tested to reduce this tumor-tolerant milieu and enable the activation of endogenous immunity against the tumor. Checkpoint inhibitors are monoclonal antibodies that block the pathways inhibiting the activation of immune cells. Several checkpoints have been identified and targeted. They include the cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programed cell death protein-1 (PD-1), T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) receptor, and lymphocyte activation gene 3 (LAG-3). Specifically, nivolumab is a fully human IgG4 antibody that blocks PD-1 and potentiates the activation of T-cells. Similarly, ipilimumab is a fully human monoclonal antibody that binds and inhibits the cytotoxic T-lymphocyte-associated antigen 4, an inhibitory receptor on T-cells. It has been noted that blocking these pathways in some individuals predisposes them to mounting immune responses to self-antigens.

Although current literature demonstrates the therapeutic promise and potential of these two new medications, they are not without significant side effects. The goal of this case report is to highlight the development of concomitant myositis and myasthenia gravis in a patient who received a combination of nivolumab and ipilimumab as a treatment of advanced metastatic melanoma.

Case Presentation

A 62-year-old female with metastatic ocular melanoma presented with generalized body weakness, pain, fatigue, and ptosis for 6 days. She had started her checkpoint inhibitor therapy with a combination of nivolumab and ipilimumab 2 weeks before symptom onset. She developed a pruritic rash on her back, hands, and chest, which had improved with topical triamcinolone 12 days prior to her presentation. At that time, she also noted progressive cramping in her thighs, lower-back stiffness, fatigue, body aches, and left-eye heaviness/droopiness. She did not report chest pain, shortness of breath, and nausea. The patient was diagnosed with left ocular melanoma in 2012 and had received intravitreal bevacizumab and radiotherapy before.

Her past medical and surgical history was noncontributory. Her family history was significant for myasthenia gravis in her grandfather and lung malignancy in her mother.

On evaluation, the patient was noted to be in a generally fair condition, except for the presence of a left-lid lag that became more pronounced on upward gaze. Application of an ice pack for 3 minutes resulted in noticeable improvement of her ptosis. Nystagmus or ocular misalignment was not noted. The patient

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had a normal visual field examination, but vertical eye movements were impaired. She was noted to have a reduced generalized muscle strength at 4/5, specifically 4/5 strength in bilateral hip flexors, on neck flexion, and in bilateral deltoids. There was weakness present with a sustained effort in these muscle groups. Reflexes were normal. The creatinine kinase level was noted to be elevated at 8994 U/L. Troponin T and I values were 0.24 ng/mL and 0.16 ng/mL, respectively. A basic metabolic profile and chest X-ray were within the normal limits. The myositis panel (Mi-2, PL-12, PL-7, EJ, OJ, Ku, SRP, U2 SnRP, Anti-PM/Scl Ab, Anti Jo-1) was negative.

Based on the above observations, a diagnosis of immune checkpoint inhibitor toxicity leading to autoimmune myositis and myasthenia gravis was made. The acetylcholine receptor antibody was positive. In the hospital, the patient received intravenous methylprednisolone 1 g daily for 3 days and intravenous fluids, leading to improved creatinine kinase levels. For myasthenia crisis, the patient was started on intravenous immunoglobulin therapy (IVIG) 2gm/kg over the next 4 days which lead to improvement in her ocular symptoms and proximal muscle weakness. Subsequently, the patient received prednisone 1 mg/kg ,which was tapered off over next 8 months. After discharge, she received IVIG 1 gm/kg every 3 weeks for 12 weeks, and then 1 gm/kg every 4 weeks for 8 weeks. At the last follow-up after 8 months of presentation, the patient had no muscle weakness or rash. Myasthenia symptoms did not recur, and the patient was off the IVIG and prednisone.

The checkpoint blockade therapy was never resumed due to the myositis and myasthenia. For hepatic metastases, the patient underwent a CT-guided liver tumor microwave ablation of the largest lesion and will undergo a chemo or chemo-immuno embolization of remaining lesions.

Literature Review

Nivolumab is an inhibitor of PD-1, which is expressed on an activated T- cells instead of T-cell. The activation of this receptor by the PD-1 ligand, usually expressed on tumor cells, leads to inactivation of the primed T-cell, leading to immunosuppression. Nivolumab decreases this inactivation, leading to an immune response against the tumor (2). Ipilimumab is a competitive inhibitor of CTLA-4. CTLA-4 inhibits the binding of B7 and CD28, a co-stimulation signal, that activates T-cell and subsequent proliferation (3).

A combination of nivolumab and ipilimumab has been shown to have a higher progression-free survival as compared to ipilimumab alone in the management of metastatic melanoma (4).

The use of checkpoint inhibitors has been shown to have numerous side effects, involving the systems of organs mainly mediated by the stimulation of an immune response that would otherwise not be elicited (immune-related adverse effects) (1-3). The most common Grade 3-4 adversely involved systems include the gastrointestinal, cutaneous, and endocrine systems. Less common was the development of neuromuscular complications.

Immune-therapy-related myositis is a notable adverse effect reported in the literature in association with ipilimumab monotherapy, nivolumab monotherapy, and a combination of both (5-9). In most of the cases, the patient presented with elevated creatinine kinase levels with an associated neuropathy, myasthenia gravis, or rhabdomyolysis. Steroids led to a rapid decline in creatine kinase and, subsequently, the resolution of myalgia.

Myasthenia gravis is an autoimmune disorder characterized by the presence of antibodies against the signaling proteins in the post-synaptic junction. The acetylcholine receptor antibody was found in all the cases of myasthenia gravis related to the use of checkpoint inhibitors (6, 8, 9). The symptoms in these cases ranged from mild muscle fatigue in appendicular muscle groups to more severe symptoms like dyspnea and dysphagia. The patients all received conventional systemic therapy including IVIG, pyridostigmine, and steroids. In some cases, plasmapheresis was also beneficial.

Other immune-related neurological adverse events include the development of Guillain–Barré syndrome (10) and transverse myelitis (9).

Conclusion

Due to a significant overlap of symptoms caused by the checkpoint inhibitors and the previous chemotherapeutic regimens and oncological progression of the tumor, extensive investigation is required to discern other etiologies. The treatment of all these adverse effects was based on clinical judgment of the provider and severity of symptoms. Grade 1-2 adverse effects from immunotherapy can be managed with continuation of therapy with the addition of low-dose steroids whereas Grade 3-4 adverse effects have been managed with discontinuation of immunotherapy, nd steroids and disease modifying agents.

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