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Atezolizumab-Induced Bell's Palsy in a Patient With Small Cell Lung Cancer

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Abstract

Immune checkpoint inhibitors are rapidly becoming popular therapeutic options for patients suffering from a number of malignancies. Atezolizumab is a programmed cell death ligand-1 inhibitor, and binding to this ligand decreases the ability of tumor cells to evade the immune system, resulting in self-tolerance. While inhibition of these molecules leads to increased T-cell destruction of tumor cells, it also may lead to autoimmune destruction of healthy cells. Neurotoxicity is a rare complication of immune checkpoint inhibitor therapy, and facial palsy as a complication of atezolizumab therapy has only been reported in one additional study. We present the case of a 68-year-old female with a history of small cell carcinoma of the lung presenting with sudden-onset facial palsy and numbness of the distal extremities in the setting of receiving atezolizumab immunotherapy. Our patient was managed with temporary cessation of her immunotherapy, oral prednisone, and supportive measures. Within 4 weeks, the patient had complete resolution of her facial palsy and was able to resume immunotherapy without further complication. Clinicians should be aware of this rare adverse effect in order to enact early management including temporary cessation of therapy to prevent morbidity in patients undergoing immunotherapy.

Keywords

immune-related adverse events, atezolizumab, Bell's palsy

Case Report

A 68-year-old female presented to the emergency department with a 2-hour history of right-sided facial droop and numbness. The patient had an extensive past medical history significant for 50-pack-years of smoking and recently diagnosed chromogranin positive, synaptophysin positive, CK7 and TTF-1 positive, small cell carcinoma of the lung in October 2019. Staging positron emission tomography-computed tomography (PET-CT) at that time demonstrated PET-avid lesions in the left upper lung lobe, left hilar lymph node, and multiple nodes in the subcarinal area. Additionally, a PET-avid lesion was seen in the liver consistent with metastatic disease. Magnetic resonance imaging of the brain was performed with no evidence of cerebral metastasis. The patient was started on chemotherapy/immunotherapy consisting of carboplatin, etoposide, and atezolizumab. After 4 cycles, the patient had a repeat CT scan of the chest/abdomen/pelvis with contrast in January 2020, which demonstrated complete response to the current therapy. A repeat CT scan of the head without contrast was also performed at that time, with no evidence of metastasis. The patient continued single-agent immunotherapy with atezolizumab. In February 2020, during a routine office visit, the patient endorsed blurring of her vision in the right eye. She visited an ophthalmologist, and further evaluation revealed that the patient was suffering from neovascularization of the retina with some associated retinal hemorrhage. At that time, immunotherapy was temporarily discontinued. The patient received one ocular bevacizumab injection; however, her repeat appointment for a second injection was cancelled due to the onset on the COVID-19 (coronavirus disease-2019) pandemic. Despite this, the patient reported improvement in her visual symptoms. On March 2020, the patient resumed immunotherapy. Throughout the course of treatment, the patient followed monthly with her oncologist. Regular laboratory evaluations including complete blood count, comprehensive metabolic panel, and thyroid stimulating hormone (TSH) were performed and were congruent with post-chemotherapy

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treatment. During this time, fasting glucose levels ranged between 83 and 96 mg/dL. The patient's TSH levels were within normal limits at each follow-up visit. The patient received a total of 5 cycles of atezolizumab immunotherapy, with her last session being 2 weeks prior to arrival to the emergency room.

On arrival to the emergency department, the patient was alert and oriented; however, she displayed left-sided facial weakness and numbness involving the forehead. On examination, the patient demonstrated inability to raise the left eyebrow or generate wrinkles on the left side of the forehead. She demonstrated an inability to close the left eye, in addition to drooping of the corner of the mouth with loss of the left nasolabial fold. There was no evidence of vesicular eruption consistent with herpes simplex virus or varicella zoster virus reactivation. Rapid HIV testing was done and was negative. Initial CT scan of the head without contrast was negative for acute bleeding. Comprehensive metabolic panel revealed no abnormalities. Serum calcium level was 9.1 mg/dL and vitamin D level was measured at 13 ng/mL (reference range 25-80 ng/mL). TSH, B_{12}, and folate levels were all within normal limits. CT-angiogram of the head and neck were also performed, showing no evidence of thrombotic occlusion. Because of the patient's history of malignancy, the decision was made to admit the patient for extensive neurologic evaluation. Magnetic resonance imaging of the head without contrast showed no abnormalities. Echocardiogram was also ordered, showing no evidence of valvular or septal abnormality with no intracardiac thrombus and normal ejection fraction of 65%. Lyme titers were ordered and were unremarkable. Rapid plasma reagin was done and was nonreactive (reference range: nonreactive). The patient was ultimately diagnosed with Bell's palsy, and was started on a 14-day tapering course of oral prednisone, starting at 60 mg, along with supportive measures, including an eye patch and artificial tears. Her immunotherapy was temporarily discontinued. Four weeks later, the patient's symptoms had completely resolved, and she once again was continued on maintenance atezolizumab therapy without further complications.

Discussion

Immunotherapy has rapidly become a very effective therapeutic option for patients with a variety of malignancies, largely due to success in clinical trials over the last decade.[1] Tumor cells are often able to escape immunologic detection due to several mechanisms, including activation of immune checkpoint molecules, which prevents antitumor T-cell responses.[2] In healthy cells, immune checkpoint molecules work through negative regulation of the immune system and promotion of self-tolerance to healthy human cells.[3] Immune checkpoint inhibitors, therefore, block these pathways that can be promoted by tumor cells and decrease self-tolerance, ultimately leading to increased antitumor responses by T-cells. There are currently 3 classes of immune checkpoint inhibitors that are approved for use in the treatment of various malignancies. These include the cytotoxic T-lymphocyte antigen 4 inhibitors, programmed cell death-1 inhibitors, and the programmed cell death ligand-1 inhibitors.[3] Because these drugs work to decrease self-tolerance, immune-related adverse events (irAE) have been reported as potential side effects of these therapies.[3] These adverse events have been shown to affect a number of organ systems including endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and neuromuscular systems.[3-5]

Neurotoxic complications as a result of immune checkpoint inhibitor therapies occur in roughly 1% of patients, according to a meta-analysis by Wang et al.[6] There are multiple hypotheses as to why immune checkpoint inhibitors may cause neurotoxic irAE. First, it has been suggested the inflammation of the endoneurial microvasculature may cause neurotoxicity, secondary to both local edema leading to neural compression, in addition to damage secondary to nearby inflammation.[7,8] Additionally, inhibition of the immune checkpoint molecules may lead to autoimmune neurologic damage secondary to unregulated T-cell activation against nerves.[8] While the mechanism remains incompletely understood, clinicians should be aware of these potential adverse events in order to enact early management strategies to prevent significant morbidity in patients using these therapies.

Atezolizumab is a programmed cell death ligand-1 inhibitor that is Food and Drug Administration approved for the treatment of lung cancer.[9] One meta-analysis described the most common side effects of atezolizumab and the percentage of patients affected, which included fatigue (24.5%), decreased appetite (13.2%), nausea (12.3%), diarrhea (10.8%), fever (10.7%), cough (9.5%), edema (8.6%), and rash (8.4%).[10] Facial palsy secondary to immune checkpoint inhibitor therapy is rare, occurring in only 5 of 364 patients in one retrospective study.[4,5] Of these 5 patients, only one was receiving atezolizumab.[4,5] Atezolizumab has been shown to cause uveitis in previous reports; however, a thorough literature review revealed only one additional case of atezolizumab-induced facial palsy.[4,5,9] Side effects secondary to immunotherapy typically occur within weeks to months of beginning therapy.[9] The American Society of Clinical Oncology have released guidelines for physicians regarding the management of neurologic irAE.[11] For patients suffering from cranial nerve palsies, it is recommended that initial workup include screening for diabetes, B_{12}, folate, TSH, and HIV.[11] Management recommendations include temporary discontinuation of immune checkpoint inhibitor therapy until resolution of symptoms.[11] In addition, it is recommended that prednisone 0.5 to 1 mg/kg be initiated for treatment.[11] Similar therapies have been initiated in a number of reported cases, which have all led to clinical improvement of symptoms.[4,5,12]

In the current case, our patient suffered from facial palsy in the context of being treated with atezolizumab immunotherapy. While neurologic events have commonly been reported

as paraneoplastic syndromes in patients suffering from small cell lung carcinoma, the patient in the current case had evidence of achieving complete remission.[13] Because of this, it is highly unlikely that her symptoms were secondary to a paraneoplastic syndrome. The patient had been following regularly with her oncologist, and laboratory evaluations during these visits, in addition to the emergency department, showed no evidence of diabetes or thyroid dysfunction. Furthermore, multiple imaging studies along with normal calcium and decreased vitamin D made sarcoidosis unlikely. The patient also had normal B_{12} and folate levels, and no evidence of herpes simplex virus or varicella zoster virus reactivation. Given the clinical picture of facial palsy with a normal neurologic evaluation, it is probable that the patient's condition was secondary to atezolizumab-induced peripheral neuropathy. Furthermore, discontinuation of atezolizumab and treatment with steroids led to resolution of the patient's symptoms.

Conclusion

Facial palsy is a rare side effect of immune checkpoint inhibitor therapy with atezolizumab. Furthermore, facial palsy has been previously described as an irAE secondary to atezolizumab in only one retrospective study. The diagnosis of facial palsy secondary to immune checkpoint inhibitor therapy is one of exclusion, and clinicians should be aware of this as a potential adverse event. Treatment includes cessation of therapy in addition to steroids and supportive measures. Due to the rarity of this side effect, further research is necessary to determine whether there are risk factors for clinicians to monitor that may predispose patients to the development of facial palsy.

Author Contributions

All authors have contributed equally to the study.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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