Bilateral Sensorineural Hearing Loss Associated With Nivolumab Therapy for Stage IV Malignant Melanoma

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Abstract

Objectives: Present the case of a 67-year-old male with stage IV malignant melanoma who presented with uveitis and sensorineural hearing loss (SNHL) while on nivolumab and review the literature for likely etiologies. Methods: A retrospective case review was conducted. The current literature was accessed to inquire about possible pathologic mechanisms and treatment options. Results: A 67-year-old male with stage IV malignant melanoma was treated with nivolumab. During therapy, the patient presented with bilateral uveitis, vertigo, and bilateral moderate sloping to moderate–severe SNHL. After 4 cycles of nivolumab, restaging scans showed no evidence of disease. Nivolumab was discontinued. The patient was placed on a 3-week course of systemic high dose steroids and topical steroid eye drops. Both his uveitis and SNHL resolved after treatment. Nivolumab enhances the antitumor activity of T cells by inhibiting the programmed death-1 receptor. While nivolumab has shown great promise in the treatment of many types of cancers, it has also been associated with many autoimmune side effects. We propose the etiology of this 67-year-old male’s SNHL and uveitis are the result of an autoimmune process secondary to an augmented T cell response induced by nivolumab. Conclusion: While immunotherapeutic agents such as nivolumab have shown great promise in the treatment of cancer, one should maintain an awareness and caution of autoimmune side effects such as uveitis and SNHL.

Keywords

nivolumab, immunotherapy, sudden sensorineural hearing loss, uveitis

Introduction

Immunotherapy has revolutionized the treatment for many end-stage cancers. Nivolumab, an anti-Programmed Death-1 (anti-PD-1) antibody, has specifically shown promise in treating metastatic malignant melanoma. While nivolumab has successfully been used to prevent further progression of metastatic disease and, in some cases, completely cure people of their end-stage disease, it has also been associated with many autoimmune side effects. Secondary conditions such as autoimmune hemolytic anemia, thyroiditis, type 1 diabetes, uveitis, sialadenitis, polyarthritis, myocarditis, and acute demyelinating encephalitis among others have been reported.1-6 In fact, a significant proportion of patients (70%) receiving anti-PD-1 immunotherapy develop some degree of autoimmune sequela, while fewer than 10% of patients experience a severe autoimmune side effect.5

Though many opportunistic autoimmune side effects have been reported in the literature, autoimmune inner ear disease and sudden sensorineural hearing loss (SNHL) is not well described. To the authors’ knowledge, there is only one article that presents the case of autoimmune SNHL caused by pembrolizumab, another anti-PD-1 monoclonal antibody, during the treatment of metastatic malignant melanoma.7 Here, we present what we believe is the first case of a patient who had...
bilateral, autoimmune-mediated SNHL while receiving nivolumab immunotherapy.

**Case Report**

A 67-year-old male with a past medical history of sarcoidosis in the 1980s presented to Upstate Cancer Center clinic for a second opinion regarding newly discovered widely metastatic melanoma with liver, bone, and adrenal metastasis. The patient had a history of a melanoma in situ diagnosed in 6 years prior which was excised with negative margins. A month prior to his clinic visit, he noted worsening dyspepsia and chest discomfort. He presented to the emergency department where an abdominal ultrasound showed multiple liver lesions and an abdominal computerized tomography (CT) scan showed lesions in the liver and adrenal glands. A core needle biopsy of the liver confirmed metastatic melanoma. A positron emission tomography (PET) and CT scan showed extensive metastasis with bone involvement in the mandible, ribs, spine, liver, and adrenal glands. At presentation, the patient complained of fatigue, diffuse bone pain, myalgia, abdominal discomfort, abdominal bloating, and constipation.

Subsequent laboratory results were positive for the proto-oncogene BRAF and Programmed Death-1 ligand-1 (PD-L1) molecular markers. The decision was made to proceed with nivolumab monotherapy as the phase 3 CheckMate 067 study had shown no added benefit from combination immunotherapy in a subgroup which was positive for PD-L1. The patient began monotherapy with nivolumab with a plan for 12 cycles of therapy. After the second cycle of therapy, he was admitted to the hospital for uncontrolled back pain. Ten days later, he was discharged on an adequate pain regimen.

The patient was tolerating infusions well until he presented to the emergency department a month later complaining of light sensitivity in both eyes. An ophthalmologic examination showed bilateral anterior uveitis and diffuse patchy posterior synechiae. The patient was started on topical atropine 1% twice daily.

He was seen at the ophthalmology clinic in the days to follow. The patient’s symptoms were mildly improved, and his eye examination was stable compared to 3 days prior. At this point, it was unclear whether intraocular inflammation was secondary to his underlying sarcoidosis or rather induced by nivolumab. The patient was started on corticosteroid ophthalmic drops and further serology workup was obtained, including angiotensin converting enzyme (ACE) level.

Shortly after the development of light sensitivity, the patient began to have symptoms of bilateral ear fullness, subjective hearing loss, and brief episodes of vertigo with sudden head movement. His primary care referred him to an otologist. Otolaryngoscopy showed intact tympanic membrane with no effusion and normal appearing landmarks. Dix-Hallpike was negative bilaterally. Patient had type A tympanograms and his audiogram showed bilateral, moderate sloping to moderately severe SNHL (Figure 1). Given the proposed autoimmune
etiology, the decision was made to start the patient on oral steroids. The patient was placed on 60 mg of oral prednisone daily for a week. The second week the patient took 40 mg daily. A taper of 10 mg each week was then used from the third week through the fifth week.

The patient was seen by his oncologist and though source of intraocular inflammation and hearing loss were unknown, nivolumab was put on hold. There was a plan to restart immunotherapy when the symptoms abated.

On subsequent follow-up, he subjectively noted a 90% improvement in his vision and an 80% improvement in his hearing. He noted only a modest improvement in his constant disequilibrium. On examination, there was improvement in intraocular inflammation, the infectious workup was negative, and ACE levels were in the normal range. Otoscopic examination was normal. His audiogram at the time showed a right mild sloping to moderate SNHL and a left a mild sloping to moderately severe SNHL (Figure 2). Given the negative serologic workup, the uveitis and SNHL were presumed to be nivolumab-induced.

After discussion with the oncology team, the decision was made to discontinue nivolumab therapy after a total of 4 cycles. Restaging magnetic resonance imaging brain and full body PET with CT scans showed that all previously seen lesions were nondetectable, and there was no evidence of metastatic disease.

The patient followed up 4 months later and reported that his hearing had returned to baseline. His audiogram at the time showed normal hearing in both ears to about 4 kHz with bilateral, mild sloping to moderate, and moderate severe high-frequency SNHL for the right and left ears respectively (Figure 3). During the interim, the patient’s chronic disequilibrium resolved, and the patient developed positional vertigo relieved with repositioning maneuvers. Repeat PET with CT confirmed no evidence of melanoma recurrence.

**Discussion**

We present 67-year-old male with stage IV metastatic melanoma who underwent successful treatment with nivolumab that was complicated by SNHL and uveitis. After a thorough investigation, it was concluded that the etiology of the patient’s uveitis and SNHL was likely from an autoimmune-mediated process secondary to the anti-PD-1 antibody nivolumab. Despite the fact that there are widespread reports of systemic side effects related to immunotherapy, autoimmune SNHL from immunotherapy is not well described. To the authors’ knowledge, this is the first report of nivolumab-mediated SNHL.

Programmed Death-1 ligand-1 is one of the many ligands that some tumor cells express to inhibit T-cell activation.
Binding of the PD-1/PD-L1 complex results in T cell apoptosis, inhibition of cytokine production, and immunosuppression which in turn allow tumor survival and growth.\textsuperscript{5,9,10} Anti-PD-1 monoclonal antibodies (such as nivolumab and pembrolizumab) bind the PD-1 receptor on lymphocytes and prevent lymphocyte inhibition, which allows for activation of cytotoxic T-cell response and potentiation of an antitumor response. While the end result is often excellent tumor control or eradication, the anti-PD-1 monoclonal antibodies are unable to differentiate between T-cells interacting with cancer cells and T-cells interacting with host cells. Given this mechanism, it is no surprise that a significant proportion of healthy patients who undergo immunotherapy have autoimmune-related side effects that affect many different systems (endocrine, cardiac, hematological, musculoskeletal, and rheumatological, among others)\textsuperscript{5}.

The pathogenesis for immunotherapy-induced autoimmune uveitis is thought to be the result of targeting nonpathological melanocytes that contain similar antigens.\textsuperscript{4} Melanocytes are located within the stria vasularis of the inner ear and are vital for normal stria vascularis development and function.\textsuperscript{11} The stria vascularis is essential for maintaining the endocochlear potential.\textsuperscript{12} Other studies that have engineered T-cells to have a high affinity for the melanoma antigens MART-1 and gp100 (termed adoptive cell immunotherapy) have reported SNHL in about half of patients.\textsuperscript{13,14} Any immunologic targeting of metastatic melanoma cells throughout the body will target melanoma-specific antigens, such as MART-1 and gp100, which are also found on the melanocytes within the stria vascularis. Like immunotherapy-induced autoimmune uveitis, melanocytes residing in the stria vascularis may also serve as a nonspecific target of immunotherapy. The collateral damage that occurs at the stria vascularis with the attack of melanocytes may disrupt the endocochlear potential, altering normal cochlear hair cells function and resulting in hearing loss. Vogt-Koyanagi-Harada disease has a similar pathogenesis where Th1 cells are thought to target melanocytes of the eye, inner ear, skin, and hair. Patients with this disease can present in a similar manner with uveitis, SNHL, and vitiligo.\textsuperscript{15}

Given the proposed mechanism for nivolumab-induced SNHL, it is interesting to consider the possibility that the type of cancer treated with immunotherapy may alter a patient’s risk of specific immunotherapy-related side effects. There is evidence that patients who experienced vitiligo after pembrolizumab for the treatment of melanoma had higher rates of complete or partial response, improved progression-free survival, and improved overall survival.\textsuperscript{16,17} This suggests that a more robust response to immunotherapy not only results in improved cancer treatment but a higher likelihood for specific side effects. This hypothesis of organ-specific adverse events has previously been discussed in the literature.\textsuperscript{18,19} At this time, there are no large studies that have associated specific adverse reactions with specific cancers to the authors’ knowledge. This represents an area that future research may be better able to access. As in the aforementioned case, a patient with melanoma being treated with nivolumab may be at a higher risk to develop
side effects in tissues with high melanocytic antigens (eyes, inner ears, or skin) given the increased T-cell affinity which could result in SNHL, uveitis, or vitiligo.

Steroids have long been used to attenuate the immunologic side effects on end organs. Zibelman et al reported the case of an 82-year-old male with primary mucosal melanoma of the ethmoid sinus treated initially with ipilimumab (CTLA-4 inhibitor) followed by pembrolizumab (anti-PD-1 monoclonal antibody) who had sudden onset bilateral mild to moderately severe symmetric SNHL. This patient was treated with intratympanic injections of dexamethasone with improvement of hearing over the following weeks. The benefit of intratympanic injections is that they can provide a site-specific immunosuppression without compromising the systemic elimination of disseminated cancer. Systemic therapy was used in our patient because the topical corticosteroid steroid eye drops were ineffective and the patient subsequently presented with a hearing loss. It is important to consider the risks and benefits of systemic steroids, particularly in patients undergoing immunotherapy for malignancy. Systemic steroids have a known immunosuppressive effect which can theoretically reduce the immune system’s targeting of healthy melanocytes before irreversible damage could take place. Systemic immunosuppression can also inhibit the targeting of melanoma tumor cells and therefore risks a reoccurrence of cancer. Fortunately, our patient was able to benefit from systemic steroid therapy without the consequence of cancer reoccurrence.

While the mechanism of action of steroids is attractive in countering the immunogenic side effects of adoptive cell immunotherapy or nivolumab/ipilimumab immunotherapy, it is important to be critical in weighing the risks and benefits of steroid use in patients with a stable or regressing disease burden. While the risks of steroid administration are well understood, the anticipated benefits steroids provide are less clear. A previous study by Seaman et al showed 17 of 32 patients had post adoptive cell immunotherapy hearing loss. Of the 17 patients who experienced hearing loss, 7 (41.2%) received no intratympanic steroids but recovered their baseline hearing, 5 (29.4%) received intratympanic steroids and recovered their baseline hearing, and 5 (29.4%) received intratympanic steroids but did not recover their baseline hearing (4 had partial return to baseline and 1 had no improvement). Only 50% of the patients who received intratympanic steroids had recovery of their hearing loss to baseline (5 of 10). In the study by Johnson et al, of 20 patients who received MART-1 targeted T cells, 10 patients had hearing loss, but all recovered to their baseline hearing (7 of 10 received intratympanic dexamethasone). Of 16 patients who received gp100 targeted T cells, 5 had mild hearing loss and 4 recovered to their baseline hearing (the only patient who received intratympanic steroids did not recover to baseline). Unfortunately, there are no other studies that compare the effect of systemic or intratympanic steroids in preventing or recovering autoimmune-induced SNHL. Given the data that is available, it is difficult to conclude that steroid administration results in a better prognosis of hearing recovery compared to observation alone and offers an opportunity for further research.

In conclusion, we present what we believe is the first reported case of a patient who had bilateral autoimmune-mediated SNHL while receiving nivolumab immunotherapy. Anti-PD1 agents such as nivolumab have provided a significant step forward in combating disseminated malignant melanoma but also carry the risk of autoimmune side effects such as SNHL. Nivolumab-enhanced T-cell response against melanoma tumor cells may result in collateral damage to other melanocytes in the eyes, stria vascularis of the inner ear, or skin resulting in autoimmune side effects. Currently, there is no strong evidence that suggests steroid therapy improves hearing outcomes in patients who have immunotherapy-induced SNHL. Therefore, the risks and benefits of intratympanic or systemic steroid therapy to preserve hearing must be weighed individually.

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