

Research Article

Audiovestibular Toxicity Secondary to Immunotherapy: Case Series and Literature Review

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ABSTRACT

Introduction: Audiovestibular toxicity secondary to immunotherapy has only rarely been reported in the literature. Herein, we examine our experience diagnosing and managing audiovestibular immune-related adverse events (irAEs) in patients undergoing immunotherapy. **Methods:** Four patients who experienced irAEs were included. Demographics, immunotherapy regimen, diagnostic tests, treatment, and outcomes were recorded in a retrospective chart review. **Results:** The cases of three patients with metastatic melanoma and one patient with metastatic renal cell carcinoma are presented. Hearing loss and tinnitus were the most common presenting symptoms. Immune checkpoint inhibitors (ICIs) were implicated in three cases and T-cell therapy in one case. Two of three patients (67%) treated with steroids had substantial improvements in hearing. **Conclusions:** Audiovestibular irAEs are a rare complication of immunotherapy. Suspicion for symptoms including hearing loss, tinnitus, and/or vertigo should prompt an expedient referral to the otolaryngologist for evaluation, as symptoms may improve with corticosteroid use. Hearing and/or vestibular deficits can have a substantial impact on the quality of life for affected patients, but rehabilitation options do exist.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) and T-cell therapies have revolutionized cancer treatment. Since the United States Food and Drug Administration (FDA) approval of ipilimumab in 2011, six additional ICIs have been approved including programmed death-1 (PD-1) inhibitors nivolumab, pembrolizumab, cemiplimab and programmed death ligand-1 (PDL-1) inhibitors atezolizumab, avelumab, and durvalumab. Targeting additional checkpoints with new compounds and using various combinations of ICIs and T-cell therapies with or without traditional treatment modalities ensure tremendous future potential.^[1,2]

Though overshadowed by overall treatment successes, treatment-related toxicities—known as immune-related adverse events (irAEs)—continue to emerge and are not yet as well understood as side effects caused by traditional chemotherapeutic agents. Skin, gastrointestinal, endocrine, lung, and musculoskeletal irAEs are

among the most common. Cardiovascular, hematologic, renal, neurologic, and ophthalmologic irAEs occur less frequently. Although most irAEs are relatively minor, life-threatening complications have occurred in up to 2% of patients.^[1] National Comprehensive Cancer Network (NCCN) consensus recommendations were produced to standardize recognition and management of irAEs. Despite significant progress in recognizing, classifying, and treating many irAEs, audiovestibular complications have received little attention, owing in part to their relatively low incidence. Presently, no recommendations exist within NCCN guidelines or other similar multidisciplinary panel guidelines with regard to identification and management of audiovestibular irAEs.^[1,2]

Our neurotology practice is solely within a cancer hospital and, therefore, uniquely positioned to manage patients who experience audiovestibular irAEs such as acute hearing loss, tinnitus, or vertigo. We report our experience managing four such patients with the hopes of raising awareness of these unique complications and

Table 1. Detail of included cases

Patient Age, y (Sex)	Tumor Type	ICI	Degree of Hearing Loss	Associated Symptoms	Treatment, Dose (Route)	Outcome of Hearing Loss	Patient Status at Last Follow-up
Case 1 54 (M)	Metastatic melanoma	Ipilimumab, nivolumab (4 cycles)	AU: moderate-severe SNHL; WRS 60%/68%	Vertigo, tinnitus	Solumedrol, 1 mg/kg x3 days (IV); prednisone 100 mg tapered over 1 month (PO); dexamethasone (IT); infliximab	Persistent high Hz loss; full low Hz and WRS recovery 100%/100%	Complete resolution
Case 2 65 (M)	Metastatic melanoma	Ipilimumab, nivolumab	AU: Moderate-severe SNHL; WRS 60%/75%	Uveitis, tinnitus, imbalance	Prednisone 60 mg (PO) tapered over 2 weeks	Complete recovery <2000 Hz, mild-moderate persistent SNHL; WRS 100% AU	Complete resolution
Case 3 58 (M)	Renal cell carcinoma	Ipilimumab, nivolumab (4 cycles)	AU: mild-moderate SNHL; WRS unaffected	Myositis, hypophysitis, headache, optic neuritis	Prednisone 90 mg (PO) tapered by 10 mg 72 hours	Unchanged hearing loss	Persistent/stable disease
Case 4 39 (F)	Metastatic melanoma	TIL therapy, pembrolizumab, dabrafenib, trametinib, ipilimumab, nivolumab, fludarabine, cyclophosphamide, aldesleukin	AU: severe-profound SNHL; WRS AD-20%/AS-4%	Uveitis, imbalance, aural fullness, tinnitus	Dexamethasone (IT) x2	Minimal improvement AD to WRS 48%	Dead of disease

F: female; ICI: immune checkpoint inhibitor; MAU: both ears; SNHL: sensorineural hearing loss; WRS: word recognition score; IV: intravenous; PO: by mouth; IT: intratympanic; TIL: tumor-infiltrating lymphocyte; AD: right ear; AS: left ear.

to discuss optimal management (see Table 1). All data collected were subject to The University of Texas MD Anderson Cancer Center's Institutional Review Board approval (IRB PA19_0106). A waiver of informed consent was obtained from the IRB for this protocol.

CASES

Case 1

A 54-year-old man with history of stage IA cutaneous melanoma initially treated with wide local excision and negative sentinel lymph node biopsy presented to the emergency room 6 years after treatment with diplopia and lateral gaze palsy. The patient was found to have a left lateral rectus lesion along with several other distant metastatic lesions. Radiation therapy was performed for the lateral rectus lesion followed by administration of four cycles of ipilimumab and nivolumab over 10 weeks. Four weeks after completion, the patient presented with complaints of imbalance, tinnitus, and rapidly progressive bilateral hearing loss. He was admitted for workup to rule out stroke and infectious etiologies. Repeated magnetic resonance imaging (MRI) showed new scattered T2 hyperintensities, which were considered reactive, as well as resolution of the lateral rectus mass. He was ultimately referred to the otology service.

An audiogram revealed bilateral moderate to severe sloping low- to high-frequency sensorineural hearing loss (SNHL) with speech recognition scores of 68% in the left ear and 60% in the right ear. He was started on intravenous (IV) methylprednisolone 1 mg/kg/day and noted immediate improvement in his hearing, vertigo, and gait. He was discharged 3 days later and transitioned to oral prednisone 1 mg/kg/day for 1 week, tapered over 30 days.

Subsequent MRI 1 month later revealed resolution of prior enhancement but new hyperintensities in the right globus pallidus and mild enhancement in the right internal auditory canal. He was thus started on a second tapering course of oral prednisone 1 mg/kg/day for 1 week tapered over 2 weeks. Repeated audiogram was stable. The patient was seen 4 weeks later and again had complaints of worsening hearing and tinnitus. Audiogram confirmed bilateral mild sloping to severe SNHL, and a third oral prednisone taper was given followed again by resolution of symptoms. He experienced a third and final episode of hearing loss bilaterally 2 weeks after receiving his third course of oral steroids. He was treated with one intratympanic injection of dexamethasone 24 mg/mL in each ear and oral steroids 1 mg/kg/day tapered over 4 weeks. He was also started on infliximab 5 mg/kg with plan to repeat dosing. Audiograms at 2 weeks and 8 months showed significant hearing recovery.

Case 2

A 65-year-old man with widely metastatic melanoma was treated with surgery and radiation followed by

initiation of ipilimumab and nivolumab around a month prior to presentation to our clinic. He presented with bilateral sudden sensorineural hearing loss, tinnitus, imbalance, and uveitis. His audiogram showed a bilateral moderate sloping to severe sensorineural hearing loss and word recognition scores (WRSs) were 60% and 75% on the right and left, respectively. He was treated by ophthalmology for uveitis, which ultimately resolved. He was treated with 60 mg PO (by mouth) prednisone for 2 weeks, and his hearing showed dramatic improvement within 3 weeks. His hearing returned to normal below 2000 Hz and showed persistent mild to moderate SNHL at high frequencies. His WRSs returned to 100% bilaterally. His disease showed a complete response.

Case 3

A 58-year-old man with recurrent renal cell carcinoma metastatic to lungs and bones was on his fourth cycle of ipilimumab and nivolumab when he developed myositis, hypophysitis, headache, optic neuritis, and hearing loss. His immunotherapy was discontinued at this time, and he was treated with oral prednisone starting at 90 mg and tapering by 10 mg every 72 hours. With the exception of his hearing loss, his other symptoms resolved over time.

Although his hearing loss occurred suddenly, he was referred to the neurotology service 5 months later. An audiogram showed mild to moderate sensorineural hearing loss. No prior audiogram was available for comparison. He received no additional treatment owing to the elapsed time since the start of his hearing loss. On a subsequent audiogram, his hearing loss did not improve. He had stable disease on his most recent follow-up.

Case 4

A 39-year-old woman with widely metastatic melanoma to brain, spleen, lung, liver, and bone was treated with surgery, radiation, and multiple chemotherapeutic agents several years prior to presenting to our clinic. She presented with acute vision change, hearing loss, and vertigo approximately a month after initiating T-cell therapy along with fludarabine, cyclophosphamide, and aldesleukin. MRI ruled out intracranial disease as a cause of her deficits. Her hearing loss was severe to profound bilaterally, and WRSs were 20% and 4% on the right and left, respectively. She was treated by ophthalmology for uveitis, which ultimately resolved. She was treated with two bilateral intratympanic (IT) dexamethasone injections for her hearing loss. Her right ear improved only slightly. Her left ear hearing remained unchanged. She ultimately died from progression of her disease.

DISCUSSION

The true incidence of irAEs is still being determined, with a wide variation in currently reported ranges from 15–90% depending on the agent and trial.^[1,2] Audio-

vestibular irAEs are extremely rare, reflected by the paucity of case reports in the literature. Patients may present with isolated audiovestibular complaints of sudden onset hearing loss, tinnitus, aural fullness, imbalance, and/or true rotary vertigo. Alternatively, these symptoms may exist in conjunction with other irAEs as seen in three of four patients (75%) in the present series.

The mechanism of irAEs is not entirely clear but previous experience with adoptive cell immunotherapy (ACI) toxicity and with genetic and autoimmune disorders provide insight into potential pathophysiology. ACI relies on T-cell receptors with high anti-melanoma/melanocyte activity. Although this therapy effectively targets melanoma tumor cells, substantial overlap is possible such that melanocytes in other areas of the body are affected.^[3] The stria vascularis is a thin, vascularized tissue bed that forms the inner sidewall of the cochlea and houses the inner ear melanocytes, also known as intermediate cells. If ACI toxicity disrupts the intermediate cells, the potassium ion-rich endolymph within the scala media of the cochlea cannot be adequately maintained, effectively preventing electrochemical signaling, which provides the basis for hearing.^[4]

Intermediate cell dysfunction is similarly implicated in several genetic conditions including mutations in connexin-26, which is the most common nonsyndromic cause of hearing loss. Mutations in this protein result in a sensorineural loss similar to that which can be seen with immunotherapy toxicity. Vogt-Koyanagi-Harada (VKH) syndrome is the autoimmune analog for ACI toxicity as it results in destruction of melanocytes in the skin, hair, eyes, and inner ear, resulting in vitiligo, alopecia, vision loss, and hearing loss, respectively.^[4] It is possible that immunotherapies directed at antigens present on tumor cells and healthy melanocytes similarly explain the pathophysiology of ICI irAEs.^[4] This mechanism is supported by our experience as three of four patients experienced ocular toxicities. Alternatively, proinflammatory cytokines as a downstream effect of T-cell activation, complement-mediated inflammation, upregulation of levels of preexisting autoreactive antibodies, and endolymphatic hydrops development have been proposed.^[5]

Duinkerken et al^[5] reported a case of unilateral hearing loss suspected to be caused by ACI use. The unilateral nature of the presentation is unique given the propensity for ototoxicity related to traditional systemic agents to present bilaterally. This fact, coupled with the experience that systemic autoimmune disease such as VKH can present asymmetrically, support their view of a multifactorial pathophysiology.

Similar to other irAEs, general management for otologic-related complications is to recognize toxicity and induce immune suppression via corticosteroids. Physical examination is crucial in the setting of hearing loss, as it must be determined if the acute change is due

to fluid behind the tympanic membrane (e.g., uninfected effusion or acute bacterial otitis media) or to an inner ear cause. An audiogram will help determine the type of hearing loss and should be performed in all patients. If the issue is a middle ear effusion, then this condition can be observed until resolution, drained with or without tube placement, or treated with oral antibiotics (for acute suppurative otitis media). If an acute sensorineural hearing loss is detected, oral and/or IT steroids are recommended.

Idiopathic sudden sensorineural hearing loss (SSNHL) is relatively frequently seen in neurotology practice with an estimated incidence of around 5 to 27 cases per 100,000 people, and experience with this entity is instructive. While the pathophysiology of SSNHL likely differs from that related to immunotherapy-induced hearing loss, there is a large body of literature regarding SSNHL from which to draw treatment recommendations for audiovestibular irAEs. Generally, the goal is for steroid initiation within 2 weeks of hearing loss. Both PO and IT steroids demonstrate equivalent efficacy, based on several randomized controlled trials for SSNHL.^[6] Reports vary in efficacy, but it is anticipated that around 2/3 of patients will recover some hearing with steroid use.^[6] In the present series, 75% (3/4) of patients improved with steroids, but given the low sample size, it remains unclear if similar recovery rates are to be expected with irAEs.

There are several contraindications to consider for PO steroid administration such as poorly controlled diabetes, psychiatric disorders, osteoporosis, or other bone-related pathologies, gastritis, and more. Additionally, given the immune suppression induced by PO steroids in light of immunotherapy, IT delivery is sometimes preferred. Oral dosing is typically 1 mg/kg/day of prednisone for at least 7 days with a 7-day taper. IT dosing is typically dexamethasone 24 mg/mL. The injection is performed in clinic under an otomicroscope. The middle ear volume is typically around 0.6 mL and should be filled as much as possible to maximize the likelihood of steroid passing through the round window membrane and into the cochlea. Patients are observed in clinic for approximately 30 minutes following the injection and asked not to swallow to avoid having the steroid drain through the Eustachian tube to the back of the throat. IT injections are relatively low risk. The main complication of IT steroids is a tympanic membrane perforation, which can occur in 1% of patients. Injections are performed with a standard hypodermic needle following anesthetization of the tympanic membrane. Injections are typically offered three to four times with an audiogram before each injection to track hearing changes.

Hearing loss, tinnitus, vertigo, and imbalance can each negatively impact a patient's quality of life.^[7] That said, the decision to discontinue immunotherapy, based on the development of audiovestibular symptoms, will have to be weighed against the oncologic risks of stopping the

therapy. This is a situation that the patient, oncologist, and otologist (or otolaryngologist) should discuss together, leaving the ultimate decision to the patient.

Fortunately, effective rehabilitation options are available if hearing does not return. Hearing aids can provide amplification for mild to moderate SNHL. As hearing drops below this level, cochlear implantation (CI) may be a consideration. CI relies on the presence of spiral ganglion cells in the cochlea and, therefore, should theoretically be efficacious in this patient population. The decision to proceed with CI evaluation will depend on the patient's disease status and prognosis.

Tinnitus commonly presents with hearing loss, as it is thought to be a central phenomenon produced as a reaction to losing auditory stimulation at certain frequencies.^[7] If hearing returns, tinnitus will typically resolve. If tinnitus does not resolve, hearing aids, white noise machines, cognitive behavioral therapy, and/or antidepressants may be used.

Vertigo and imbalance are disruptive for patients. Antiemetics can be useful in the short-term, but long-term use impairs central compensation. Vestibular exercises and balance therapy are extremely efficacious and are useful to prevent falls.

At the time of manuscript preparation, only 13 cases of audiovestibular irAEs related to ICI use were reported in the literature. Rosner et al^[8] recently published the largest series to date with six patients, and the remaining cases are individual case reports.^[9-14] The indication for ICI use was melanoma for 12 cases and non-small lung cancer in one. ICIs included ipilimumab, pembrolizumab, and nivolumab. Hearing loss with or without tinnitus was the only symptom in five cases, whereas vertigo, uveitis, hypophysitis, dermatitis, arthritis, pancreatitis, and/or vitiligo were seen in the remaining cases. The hearing loss was typically bilateral and symmetric except for two cases of unilateral hearing loss and one case of asymmetric SNHL. The extent of hearing loss varied from only mild SNHL (still able to communicate without hearing aid) to severe SNHL (unable to effectively communicate). Treatment included observation or oral, IV, and IT steroids (dexamethasone, methylprednisolone, or prednisone) of variable doses and treatment duration. ICI was stopped following the irAE in 6 of the 13 cases. Symptom onset occurred following the completion of ICI in one case. In the eight patients who were treated with steroids, hearing returned to normal in two cases, was not reported in one case, and improved in each of the other five cases. In those five patients who were not treated, the hearing loss persisted. Twelve cases had a comment on tumor status with five noting complete resolution of disease, one showing a significant response but not complete tumor resolution, five showing partial response, and one with progressive disease.

Seaman et al^[3] published the largest series of audiovestibular irAEs involving 32 patients treated with adoptive T-cell therapy. Seventeen patients (53%) expe-

rienced mild or moderate hearing loss and seven (22%) had vestibular complaints. Hearing ultimately recovered to baseline levels in 12 of 17 (70%) and improved to some degree in all patients. Five of the 12 were treated with IT steroids, and the remainder were not treated. Three of the seven vestibular patients recovered to normal function. Interestingly, the authors found a dose-response relationship with hearing more susceptible than vestibular function, suggesting a differential T-cell penetration into the vestibular end organs versus the cochlea.

Several questions remain unanswered. The true incidence of audiovestibular irAEs is unclear. We advocate for inclusion in the annual NCCN irAE update to increase awareness and promote proper management. Although the exact dosing is not clear, there appears to be a benefit from management with steroids. This is in keeping with the known mechanism of immunotherapy, treatment protocols for other irAEs, and the positive response seen in the present series and the cases published to date. Several reports have suggested irAEs serve as a biomarker for treatment response, but this remains unclear. The present series involves only bilateral irAEs, whereas prior reports of unilateral complications suggest a multifactorial mechanism of injury. This needs further clarification and may have implications for management. Ideally patients should have an audiogram prior to receiving any treatment that could cause hearing loss. Clinicians should be cognizant of audiovestibular irAEs and quickly refer patients to the otolaryngologist for evaluation if suspected. Additionally, treating clinicians should be aware of the possibility of multisystem involvement in a patient presenting with audiovestibular irAEs. Concurrent ocular, dermatologic, and hair-related manifestations may exist and prompt involvement of other specialists.

CONCLUSIONS

Audiovestibular irAEs are a rare complication of immunotherapy. Suspicion for symptoms including hearing loss, tinnitus, and/or vertigo should prompt an expedient referral to the otolaryngologist for evaluation as symptoms may improve with timely corticosteroid use. Hearing and vestibular deficits can have a substantial impact on the quality of life for affected patients, but rehabilitation options do exist.

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