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Letter to the Editor

Cochleovestibular toxicity induced by immune checkpoint inhibition: a case series

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To the Editor

The prognosis of several types of metastatic cancer has dramatically improved since the advent of immune checkpoint inhibitors (ICIs) targeting the cytotoxic T lymphocyte–associated antigen 4 and the programmed death protein 1 (PD-1/PD-L1). Yet, ICI therapy is associated with frequent immune-related adverse events (irAEs), which can potentially involve every organ mimicking some inflammatory conditions [1]. Neurological irAEs occur in 3–12% of cases and include peripheral neuropathy, meningitis and encephalopathy [2]. Conversely, cochleovestibular toxicity is poorly

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described; only one case of bilateral sensorineural hearing loss with pembrolizumab has been reported to date [3].

We herein report a series of 4 cases of cochleovestibular disorders associated with ICI in patients with metastatic cancer (Table 1). Three patients received nivolumab for a non–small-cell lung cancer (n = 2) or a Merkel cell carcinoma (n = 1), and one patient received a combination of ipilimumab and nivolumab for a melanoma. The median time of cochleovestibular

Table 1
Patient characteristics.

Patient features		Patient 1	Patient 2	Patient 3	Patient 4
Sex, age (years)		Female, 63	Female, 57	Female, 69	Male, 73
Tumour history	Stage IV cancer	Merkel cell carcinoma	Non–small-cell lung cancer (adenocarcinoma)	Melanoma	Non small cell lung cancer (adenocarcinoma)
	Brain metastases	No	Yes Previously treated with WBRT	No	Yes Previously treated with SRS
	ICI; line	Nivolumab (3 mg/kg/2 weeks) 1st line	Nivolumab (3 mg/kg/2 weeks) 2nd line	Ipilimumab (3 mg/kg/3 weeks) and Nivolumab (1 mg/kg/3weeks) - 1st line	Nivolumab (3 mg/kg/2 weeks) 2nd line
Cochleovestibular toxicity	Diagnosis	Bilateral vestibular deficit	Bilateral cochleovestibular deficit	Bilateral perception hearing loss	Bilateral perception hearing loss associated with a meningitis*
	Onset of symptoms from starting ICI	After 1 month	After 4 months	After 2 months	After 14 months
	Clinical symptoms	Rotary vertigos, oscillopsia. Balance disorders, dizziness Horizontal-rotatory right spontaneous nystagmus	Balance disorders No rotatory vertigo but ataxia, dizziness and oscillopsia	Brief rotatory vertigos Bilateral hearing loss Discrete balance disorders Positional nystagmus	Asymmetrical bilateral hearing loss
	Brain MRI	Normal	Bilateral spontaneous increased labyrinthine signal on FLAIR sequence	NA	Stable sequelae of SRS
	Lumbar puncture	NA	Normal	NA	High CSF protein level (0.88 g/l), no pleocytosis*
	Cochleovestibular tests	Normal auditory evoked potentials Bilateral canalar vestibular deficit (video head impulse test)	Profound bilateral vestibular areflexia and bilateral asymmetric hearing loss	Bilateral perceptive hearing loss slightly predominant right in tonal and symmetrical in speech recognition tests	Bilateral perceptive hearing loss
	Treatment of irAE	Vestibular rehabilitation No corticosteroid No ICI discontinuation	Systemic corticosteroids (starting from 1 mg/kg/d), total duration 7 months No ICI discontinuation	ICI discontinuation for concomitant grade III hepatitis No corticosteroid	ICI discontinuation for complete response. Systemic corticosteroids (starting from 1 mg/kg/d), total duration 4 months
	Evolution of irAE	Improvement of symptoms in 1 month	Poor improvement auditory symptoms in 2 months. No improvement of vestibular symptoms after 10 months	Resolution of symptoms in 3 months	Improvement of symptoms after 1 month, then worsening 2 months after stopping corticosteroid
Other irAEs		None	None	Bilateral anterior uveitis grade II Hypophysitis grade II Hepatitis grade III	Thyroiditis
Cancer evolution		Complete response	Partial response	Complete response persisting after ICI discontinuation	Partial response persisting after ICI discontinuation

ICI, immune checkpoint inhibitor; NA, not available; SRS, stereotactic radio surgery; WBRT, whole-brain radiation therapy.
*Absence of pleocytosis was attributed to the introduction of corticosteroids 1 mg/kg/day for 5 days.

symptom onset was 3 months (1–14 months). Symptoms included balance disorders (n = 3), rotatory vertigo (n = 2), hearing loss (n = 2) and nystagmus (n = 2). Inner ear and brain MRI revealed a bilateral increased labyrinthine signal on T2-FLAIR sequence associated with a bilateral decreased utricular signal on T2 sequence in one case.

All patients underwent clinical videoscopy examination (Framiral®), pure-tone audiogram (PTA, otometrics® device), video head impulse test (VHIT; otometrics® device) and ocular and cervical vestibular-evoked myogenic potentials (otometrics® device), leading to the diagnosis of an isolated bilateral vestibular deficit (#1), a sudden bilateral and asymmetric hearing loss (#3, #4) and a bilateral cochleovestibular deficit (#2), associated with a benign paroxysmal positional vertigo (#3). For patients 1, 2 and 3, the deficit was sudden and bilateral, thus matching the autoimmune inner ear disease's criteria [4] and supporting the diagnosis of an ICI-induced cochleovestibular irAE. For patient 4, the lumbar puncture performed after 5 days of corticosteroids revealed an isolated high protein level in cerebrospinal fluid (CSF) but no pleocytosis, thus suggesting that the vestibular disorder might be associated with ICI-induced meningitis [2].

The management was heterogeneous, including ICI discontinuation (n = 2), systemic corticosteroids (n = 2) and vestibular rehabilitation (n = 1), leading to partial (n = 2), complete (n = 1) or no (n = 1) resolution of cochleovestibular symptoms. All patients had durable response to ICI.

In conclusion, cochleovestibular irAEs associated with ICI are rare and poorly described, but the risk of persistent hearing sequels requires clinicians to pay attention to symptoms such as ataxia, dizziness or hearing loss occurring during ICI therapy. A brain MRI and a lumbar puncture should be performed to rule out the differential diagnoses such as brain or leptomeningeal metastases or ICI-induced meningitis. A cochleovestibular examination including videonystagmoscopy, VHIT and PTA is required to assess the inner ear involvement. The onset of symptoms in the first months of treatment with ICI, the bilateral involvement and the lack of clinical response to the usual treatment as VBBP maneuvers support the diagnosis of an irAE. Our series suggests that cochleovestibular irAEs can occur and be managed with vestibular rehabilitation and/or corticosteroids, while ICI discontinuation is not strictly required.

Conflict of interest statement

VG reported honoraria from MSD, consulting advisory role from Astrazeneca, Roche, Boerhinger, BMS, Abbvie and travel accommodation from Pfizer. L.D. received travel expense from Roche, AstraZeneca, MSD and Pfizer. J.D. received travel accommodations from Pierre Fabre and Roche. B.B. is a consultor for BMS, MSD and Pierre Fabre. C.L. received grants or honoraria from Roche, BMS, MSD, GSK, Novartis and Amgen. A.F.C. is a consultor for BMS. The other authors have no conflict of interests to disclose.

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References

[1] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68. https://doi.org/10.1056/NEJMra1703481.

[2] Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. Eur J Cancer 2017;73:1–8. https://doi.org/10.1016/j.ejca.2016.12.001.

[3] Zibelman M, Pollak N, Olszanski AJ. Autoimmune inner ear disease in a melanoma patient treated with pembrolizumab. J Immunother Cancer 2016;4:8. https://doi.org/10.1186/s40425-016-0114-4.

[4] Ciorba A, Corazzi V, Bianchini C, Aimoni C, Pelucchi S, Skarżyński PH, et al. Autoimmune inner ear disease (AIED): a diagnostic challenge. Int J Immunopathol Pharmacol 2018;32. https://doi.org/10.1177/2058738418808680. 2058738418808680.