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OTOPATHOLOGY REPORT

Laryngoscope Investigative Otolaryngology

Cisplatin ototoxicity histopathology

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1 | INTRODUCTION

The ototoxic effects of cisplatin administration used for chemotherapy in patients with cancer as well as the effects in the inner ear in animal models are well documented.[1] However, there are few reports on the otopathological changes in temporal bone patients that have received cisplatin.

The sensory hair cells are the primary cellular substrates for this drug, although there is also evidence that the spiral ganglia neurons and the stria vascularis are also affected.[1] In the vestibular periphery, the vestibular ganglia neurons as well as the vestibular hair cells and nerve fibers are assumed to be the primary cells impacted.[2] However, histopathological evidence of this damage is very limited. In this report, we describe the temporal bone pathological changes in a patient diagnosed with Hodgkin's disease who underwent cisplatin administration.

2 | MATERIAL AND METHODS

The NIDCD National Human Temporal Bone Laboratory at UCLA (HTB) database was used to identify the temporal bones from a patient that had undergone cisplatin treatment. This study was approved by the Institutional Review Board (IRB) of UCLA (IRB protocol #10-001449). All methods used in this study were in accordance with NIH and IRB guidelines and regulations. Appropriate informed consent was obtained from each patient before inclusion in the study.

The HTBs were prepared as have been described previously.[3] The temporal bones had been removed postmortem and placed in 10% neutral buffered formalin for 3 weeks. They were then decalcified in ethylenediaminetetraacetic acid until confirmed free of calcium by X-ray imaging. The HTBs were then embedded in increasing concentrations of celloidin to allow complete penetration. The temporal bones embedded in celloidin was cut into 20-μm sections, and every 10th section of which was mounted and processed in hematoxylin and eosin stain (H&E). Each HTB microscopic section was examined first for evidence of cochlear ototoxicity in the organ of Corti, lateral wall, and spiral ganglia neurons. The temporal bone sections were then analyzed for utricular, saccular, and semicircular canal cristae ampullaris ototoxicity and pathological changes. Copies of the medical record for the patient donor were reviewed for demographic information and clinical history. Cytocochleogram and total neuronal counts of the spiral ganglion neurons were obtained as described by Schuknecht.[4] The cochlea from a 30-year-old male with normal hearing was used for cytocochleogram and comparison of spiral ganglia neuron number.

3 | RESULTS

This case involves a 29-year-old male diagnosed with stage IIIA nodular sclerosing Hodgkin's lymphoma. He was initially diagnosed at 22 years old, after undergoing a cervical lymph node biopsy. He then underwent total nodal irradiation, chemotherapy, and splenectomy

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over the consequent years. Unfortunately, his disease proved refractory to these treatments and by the age of 29, he was hospitalized for persistent disease and dysphagia. At that time, an audiogram was performed (Figure 1A), which demonstrated a mild high-frequency sensorineural hearing loss of unknown origin. He then received his first course of cisplatin 33 mg, IV TID × 4 days. He was discharged from the hospital and returned 1 month later for a second round of cisplatin. Repeat audiogram on readmission showed marked bilateral hearing loss in the high-frequency range (3000-8000 KHz) as demonstrated in Figure 1B. This was associated with intermittent tinnitus bilaterally. Given his symptoms and newfound hearing loss, cisplatin was discontinued. One month later, he was admitted to the hospital for diarrhea, rash, and persistent, decreased hearing and tinnitus. During his hospitalization, he developed acute chest pain. He was found to have a perforated esophagus and acute mediastinitis and died from associated complications.

Temporal bones were removed as described above and H&E sections were examined. The left and right sides were examined. Histopathological changes showed similar changes between the two sides. Cytocochleogram (Figure 1B1) shows the area of hair cell loss (see pathology description below). A cytocochleogram from a 30-year-old individual with normal hearing was obtained for comparison (Figure 1C).

As noted in Figure 2A, depicting a mid-modiolus section of the right cochlea, there is notable damage centered around the organ of Corti within the first half of the basal turn. This damage is characterized by notable decrease in outer hair cells (OHCs) in this region. This is more pronounced at the basal turn of the cochlea (Figure 2B), with more hair cells in the mid-basal turn (Figure 2D), with a normal number of hair cells at the apex (Figure 2C). In addition, there is congestion of the stria vascularis suggested by engorgement and dilation of vessels in this region with focal calcified structures in the basal layer of the stria (Figure 2E) and a mild decrease in spiral ganglion neurons (Figure 2F). With regard to the cytocochleogram, there were 26 500 spiral ganglia neurons in the cisplatin temporal bone and 28 000 in the normal temporal bone, both numbers between the range for this

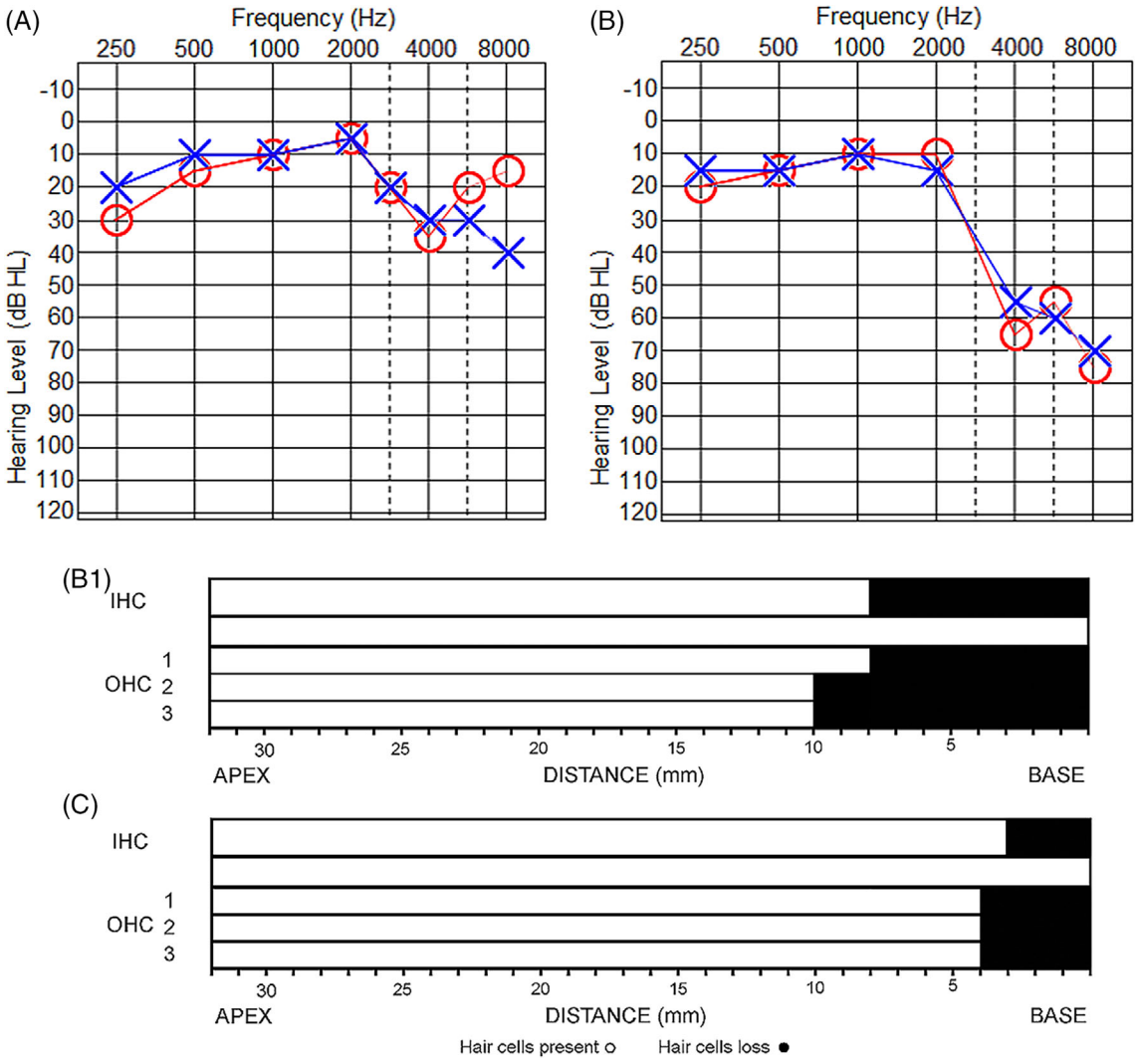

FIGURE 1 A, Audiogram before cisplatin treatment; B, audiogram after treatment; B1, cytocochleogram from the temporal bone after cisplatin; C, cytocochleogram performed on a healthy cochlea of a 30-year-old male with normal hearing

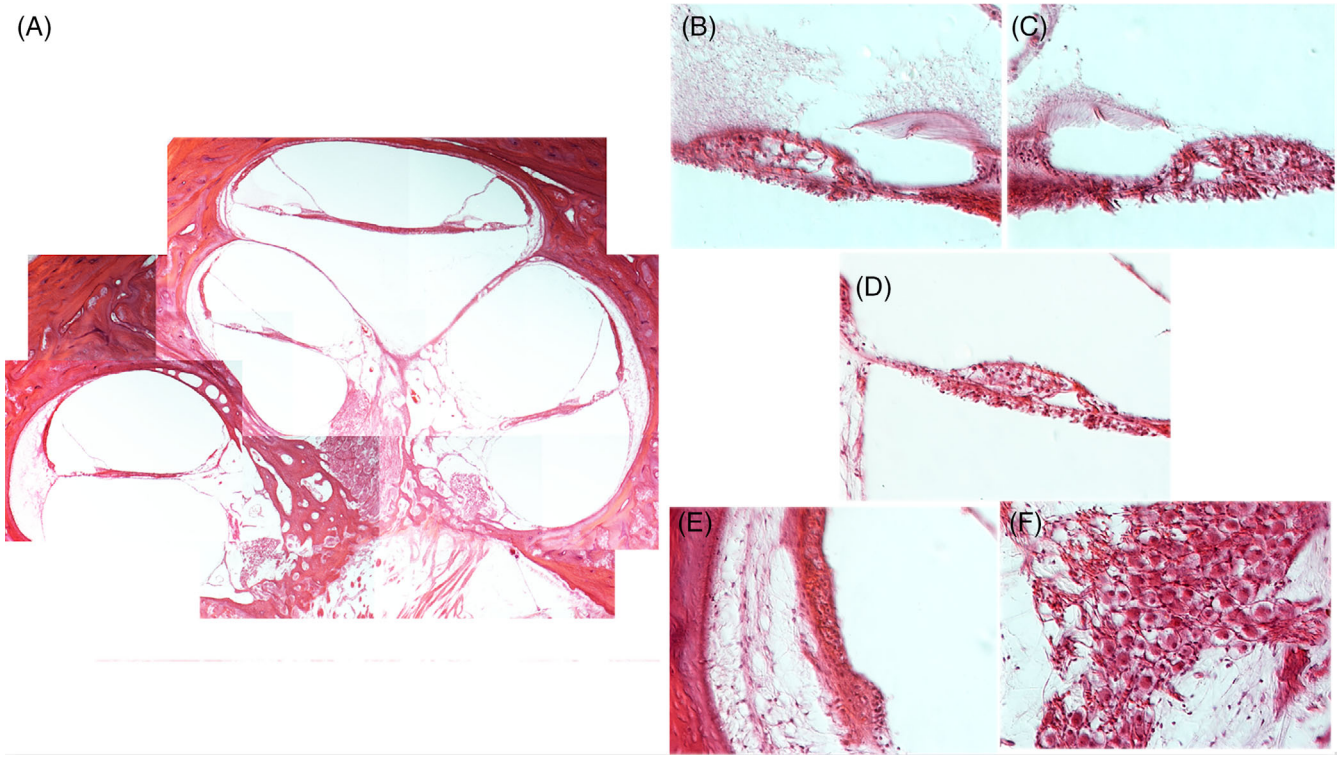

FIGURE 2 A, Mid-modiolus section of the right side temporal bone (×100 magnification); B, organ of Corti at the basal turn; C, organ of Corti at the apex; D, organ of Corti at mid-basal turn; E, stria vascularis; F, spiral ganglion cells at the basal region (×200). Hematoxylin and eosin stain (H&E) staining

age.[4] Regarding the vestibular end organs as depicted in Figure 3, the semicircular canal crista shows an almost normal organization, some thinning of the apical portion of the cristae sensory epithelium with associated healthy-appearing neural fibers (Figure 3A-C). Figure 3D,E shows the macula saccule and utricle, respectively. The sensory epithelia showed a normal organization with almost no sensory cells lost. Figure 3A1-E1 shows a higher magnification view (×400) of the sensory epithelia in each end organ represented in Figure 3A-E. We noted a remarkable preservation of hair cells in all vestibular end organs. Transition epithelial and dark cells are also normal. The stromal tissue underneath the sensory epithelium in all endorgans is also normal.

4 | DISCUSSION

We present a histopathological study of the temporal bones from a patient who received cisplatin administration. The primary ototoxic effect of cisplatin is within the cochlea, with significant damage in the organ of Corti at the base-hook region. These temporal bone findings are consistent with what has been previously reported in the literature regarding cochlear histological changes. In humans, areas of cochlear damage have been cited as the OHCs in the basal turn, the stria vascularis, and the spiral ganglion neurons.[1] These locations of ototoxic insult have been reproduced in multiple animal studies revealing similar patterns of subsequent hearing loss.[1] In our analysis, we noted similar sites of damage. The organ of Corti demonstrated notable loss of OHCs at the basal turn of the cochlea which progressively improved by the midturn and apical turns. This was confirmed by our findings on cytocochleogram (Figure 1B1). In addition, when comparing the amount of OHC loss with that of a healthy control (Figure 1C), there was a notable decrease in OHC numbers in the basal turn of the cisplatin specimen. A decrease was also noted in the number of spiral ganglion neurons between our subject when compared with the age-matched control. Additional histological changes included congestion and slight engorgement of the vessels along the stria vascularis with some areas of calcification. Overall, these changes translate to our subject's audiometric testing as he demonstrated bilateral severe high-frequency sensorineural hearing loss and associated tinnitus. Other audiological testing performed in animals would support our histological results as well. Distortion product otoacoustic emissions are diminished in gerbils after administration of cisplatin which would implicate the loss of OHCs we saw in our subject.[1] Furthermore, auditory brainstem responses in animals following treatment with cisplatin revealed increased thresholds, most dramatically in the higher frequencies which is again consistent with our findings.[1]

Histopathological analysis of our patient's vestibular end organs revealed minimal changes. The crista of the semicircular canals showed nearly normal organization. There were healthy neural fibers and normal-appearing sensory epithelia in both the macula saccule and utricle. In addition, our patient did not exhibit any vestibular

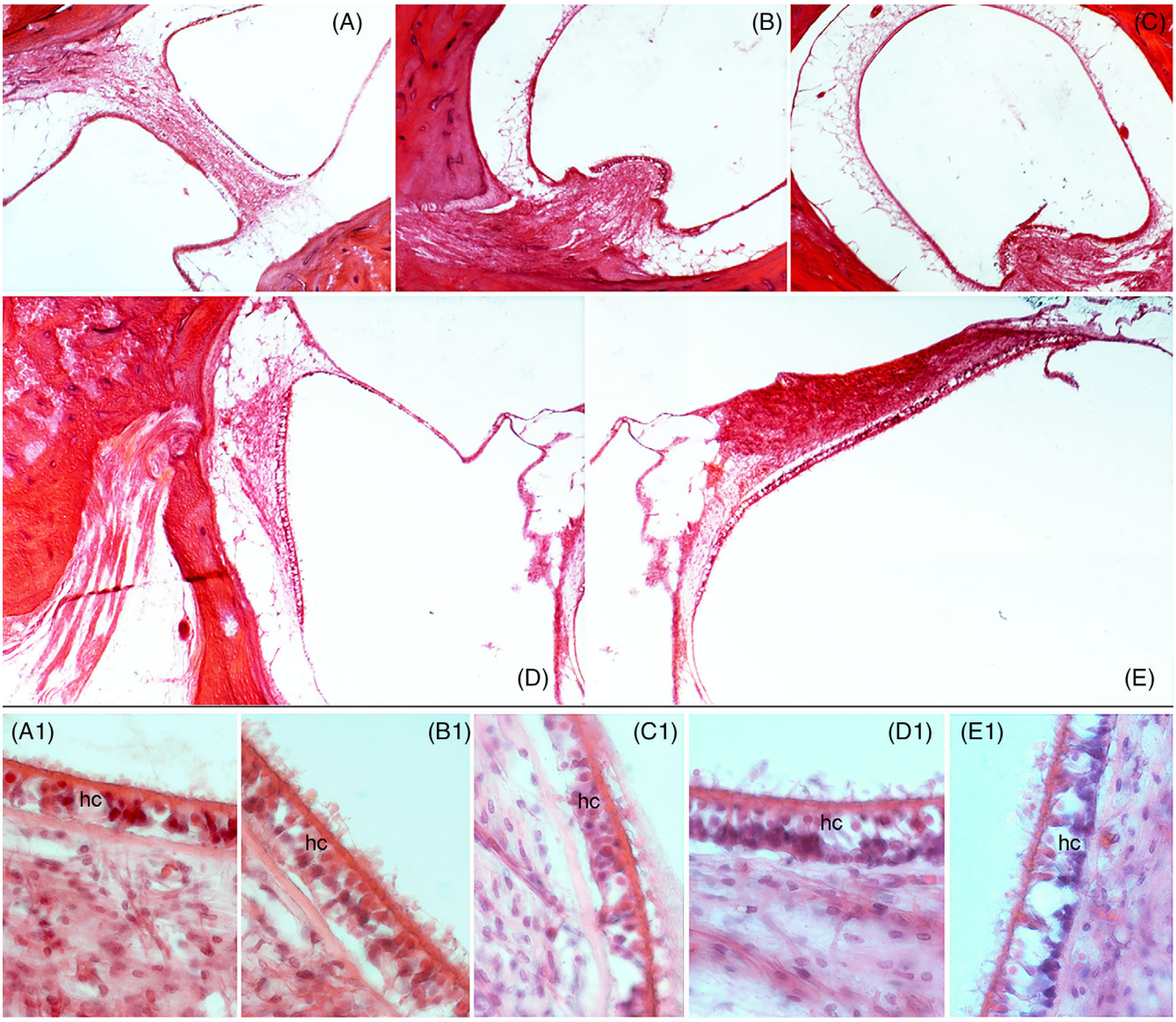

FIGURE 3 Vestibular endorgans of the right side temporal bone. A, Lateral crista; B, anterior crista; C, posterior crista; D, saccule; E, utricle. A1-E1 shows high-magnification view of the vestibular sensory epithelium; hair cells (hc) are very well preserved. ×100 magnification, A-E; ×400, A1-E1

symptoms. A review of the literature revealed that testing and evaluation of vestibular symptoms following cisplatin administration is highly variable and results did not always correlate with patient symptomatology.[2] Previous animal studies examining the histological changes within the vestibular system specifically demonstrated varying degrees of end organ damage based on the dosage of cisplatin.[2] They argue that a u-shaped curve may exist with regard to dosage and vestibular hair cell damage specifically.[2] Low and very high levels of cisplatin revealed relatively normal vestibular hair cells with the most dramatic damage seen at more intermediate doses.[2] In contrast to this, damage to vestibular nerve fibers and synapses appears to increase proportionally as the dose of cisplatin increases.[2] Given the relatively normal histological findings within the vestibular end organs in our temporal bone specimens, our study suggests that perhaps the vestibular system is more resilient to cisplatin ototoxicity or that damage severity is much more variable based on individual factors not yet known.

In conclusion, cochlear ototoxic damage caused by cisplatin in these temporal bone specimens resembles the damage reported in animal models, and continuous monitoring of hearing damage should be performed when this chemotherapy agent is administered. Despite increased variability cited in the literature with regard to vestibular ototoxicity specifically, a thorough investigation of all potential otologic side effects is warranted in patients taking this medication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest to report.

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REFERENCES

1. Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res*. 2007;226(1–2):157-167. https://doi.org/10.1016/j.heares.2006.09.015.
2. Ding D, Jiang H, Zhang J, et al. Cisplatin-induced vestibular hair cell lesion-less damage at high doses. *J Otol*. 2018;13(4):115-121. https://doi.org/10.1016/j.joto.2018.08.002.
3. Ishiyama A, Doherty J, Ishiyama G, Quesnel AM, Lopez I, Linthicum FH. Post hybrid cochlear implant hearing loss and endolymphatic hydrops. *Otol Neurotol*. 2016;37(10):1516-1521.
4. Schuknecht HF. Methods of removal, preparation, and study. In: Schuknecht HF, ed. *Pathology of the Ear. Chapter 1*. 2nd ed. Philadelphia, PA: Lea & Febiger Editorial; 1993.

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