The Laryngoscope

Temporal Bone Histopathology in Neurofibromatosis Type 2

Sung-Il Nam, MD; Fred H. Linthicum, Jr., MD; Saumil N. Merchant, MD

Objectives/Hypothesis: To describe the histopathologic findings in the temporal bone in patients with neurofibromatosis type 2 (NF2). The literature contains limited data on otopathology of NF2.

Study Design: Basic science study.

Methods: Twenty-six temporal bones from 16 patients with NF2 were examined by light microscopy. The diagnosis of NF2 was made on the basis of bilateral cochleovestibular schwannomas. Clinical information was obtained from review of the medical records.

Results: The tumors were multicentric in origin in 19 of 26 (73%) ears. Typically, tumors were seen arising within the internal auditory canal and from various locations within the labyrinth. The majority of schwannomas showed high cellularity with involvement of the labyrinth. Most cases showed significant degrees of degeneration of sensory and neural elements within the cochlea. Fusion tumors were sometimes seen as a result of a schwannoma merging with an adjacent meningioma. Fifteen of 26 (58%) ears showed facial nerve involvement by schwannoma.

Conclusions: Cochleovestibular schwannomas in NF2 are aggressive neoplasms; they are often multicentric and demonstrate a propensity to involve the labyrinth. There is often associated secondary degeneration within the cochlea. These features make total removal of these tumors and their removal with preservation of hearing more difficult than with sporadic unilateral cochleovestibular schwannoma.

Key Words: Neurofibromatosis type 2, bilateral acoustic neuroma, temporal bone histopathology, otopathology.

***Laryngoscope,* 121:1548–1554, 2011**

INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder resulting from mutations in the NF2 gene on chromosome 22q12.2.[1,2] The clinical hallmark of NF2 is the occurrence of bilateral cochleovestibular schwannomas (acoustic tumors) in virtually all individuals. Patients with NF2 may also develop other intracranial tumors such as schwannomas on other cranial nerves, meningiomas, ependymomas, astrocytomas, and glial hamartomas. We describe the temporal bone histopathology in patients with NF2 in this report. In studying NF2 cases, we have observed features such as multicentricity and involvement of the labyrinth, which are typically not seen in sporadic acoustic tumors; these and related findings have implications for the clinical management of NF2 neoplasms. Another factor that provided impetus for the present report is that the literature contains limited data describing temporal bone histopathology in NF2. Previous descriptions have consisted of one to three cases each[3–7] or reports focused on patterns of involvement of the cochlear nerve.[8,9]

From the Massachusetts Eye and Ear Infirmary and Harvard Medical School (S.-I.N., S.N.M.), Boston, Massachusetts; and House Ear Institute (F.H.L.), Los Angeles, California, U.S.A.

Editor's Note: This Manuscript was accepted for publication March 15, 2011.

This work was supported by NIH grants U24 DC008559 and U24DC008625. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Saumil N. Merchant, MD, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114-3006. E-mail: Saumil_merchant@meei.harvard.edu

DOI: 10.1002/lary.21822

MATERIALS AND METHODS

Archival temporal bones with a diagnosis of NF2 within the collections at the Massachusetts Eye and Ear Infirmary (MEEI) and the House Ear Institute (HEI) were examined. The diagnosis of NF2 was based primarily on the occurrence of bilateral cochleovestibular schwannoma. The diagnosis had been made during life in all cases except two. The temporal bones were processed for light microscopy using the standard method consisting of fixation in formalin, decalcification using trichloroacetic acid or ethylenediaminetetraacetic acid, embedding in celloidin, serial sectioning in the horizontal plane at a section thickness of 20 μm, and staining of every 10th section using hematoxylin and eosin.[10] Clinical information was obtained from the medical records, and temporal bone sections were examined using the light microscope. The respective institutional review boards of MEEI and HEI approved the study.

RESULTS

The study material consisted of 16 cases with NF2, with a total of 26 temporal bones. There were seven males and nine females, with ages ranging from 17 to 89 years. Table I displays the detailed findings in all cases. Notable highlights are summarized here.

The tumors were multicentric in origin in 13 of 16 (81%) patients (19 of 26 [73%] ears). The neoplasms arose from Schwann cells ensheathing the axons of the cochlear and/or vestibular nerves at various locations between the glial-Schwann cell junction in the internal auditory canal (IAC) and the terminations of the axons in the auditory and vestibular end organs within the labyrinth. Separate, discrete foci of tumors arose in different parts of the labyrinth in multiple cases.

TABLE I.
Clinical and Histopathologic Data of NF2 Cases.

Case No.	Sex/ Age, yr	Side	Surgery	8th Nerve Schwannoma Type	8th Nerve Schwannoma Location	Cochlear Pathology	7th Nerve Schwannoma	Fusion Tumor	Mutation in NF2 Gene (If Known)
1	M/27	R	Suboccipital	Multicentric	IAC, cochlea	Hair cell and neuronal loss, hydrops, acidophilic staining	Yes	No	
		L	Suboccipital	Multicentric	IAC, SSC	Hair cell, strial & neuronal loss, hydrops, acidophilic staining	No	No	
2	F/34	R	Transpetrosal	CNA	In surgical defect	CNA	CNA	CNA	
		L	Suboccipital	Multicentric	IAC, cochlea	Severe degeneration of all cochlear structures	Yes	Yes	
3	F/43	R	Untreated	Multicentric	IAC, cochlea, vestibule, SSC	Hair cell, strial and neuronal loss, acidophilic staining	Yes	No	Exon 9 (884 del 1 bp)
		L	Translab	Multicentric	IAC, cochlea, vestibule	Severe degeneration of all cochlear structures, hydrops	Yes	Yes	
4	M/44	R	Suboccipital	CNA	CNA	CNA	CNA	CNA	Exon 11 (C1021T, Arg341X)
		L	Suboccipital	Multicentric	IAC cochlea, vestibule, SSC	Severe degeneration of all cochlear structures	Yes	No	
5	M/70	R	Biopsy	Multicentric	IAC, cochlea, vestibule, SSC	Severe degeneration of all cochlear structures	No	No	
		L	Suboccipital	Multicentric	IAC, cochlea, vestibule, SSC	Hair cell, strial and neuronal loss, hydrops, acidophilic staining	No	No	
6	M/36	R	CNA	CNA	CNA	CNA	CNA	CNA	
		L	Translab	Multicentric	IAC, cochlea	Hair cell, strial and neuronal loss, scala tympani fibrosis	Yes	No	
7	M/41	R	CNA	CNA	CNA	CNA	CNA	CNA	
		L	Translab	Multicentric	IAC, cochlea, vestibule	Hair cell, strial and neuronal loss, hydrops	No	No	
8	M/70	R	Untreated	Solitary	IAC	No cochlear pathology	No	No	
		L	Untreated	Solitary	IAC	Neuronal loss, acidophilic staining	No	No	
9	F/89	R	Untreated	Solitary	Cochlea (modiolus)	Neuronal loss	No	No	
		L	Untreated	Solitary	Cochlea (modiolus)	Neuronal loss	Yes	No	
10	F/53	R	Translab	Multicentric	IAC, cochlea	Hair cell, strial and neuronal loss	Yes	No	
		L	CNA	CNA	CNA	CNA	CNA	CNA	
11	M/19	R	Untreated	Multicentric	IAC, cochlea, vestibule, SSC	Neuronal loss	Yes	No	
		L	Retrolab	Multicentric	IAC, cochlea, SSC	Hair cell and neuronal loss	No	No	
12	F/34	R	Retrolab	Multicentric	IAC, cochlea	Hydrops, acidophilic staining	No	No	
		L	CNA	CNA	CNA	CNA	CNA	CNA	
13	F/17	R	Suboccipital	Multicentric	IAC, cochlea	Hair cell and neuronal loss	Yes	Yes	
		L	Suboccipital	Solitary	IAC	Hair cell, strial and neuronal loss	Yes	No	
14	F/31	R	Untreated	Multicentric	IAC, cochlea, vestibule, SSC	Hair cell, strial and neuronal loss, hydrops	Yes	No	
		L	Untreated	Multicentric	IAC, cochlea, vestibule, SSC	Strial & hair cell loss, hydrops	Yes	No	
15	F/52	R	Translab	Multicentric	IAC, cochlea	Hair cell, strial, and neuronal loss	Yes	No	
		L	Translab	Multicentric	IAC, cochlea	Strial, hair cell and neuronal loss	Yes	No	
16	F/72	R	Middle fossa	Solitary	IAC	Strial and neuronal loss, neo-ossification in basal segment	No	No	
		L	Untreated	Solitary	Cochlea	Strial loss	No	No	

NF2 = neurofibromatosis type 2; M = male; F = female; R = right; L = left; IAC = internal auditory canal; SSC = semicircular canal; CNA = could not assess; Translab = translabyrinthine; Retro = retrolabyrinthine.

Schwannomas were almost always present within the IAC and were seen in 23 of 26 ears (88%). The only exceptions were small asymptomatic tumors arising within the modiolus bilaterally in a 89-year-old woman (Case 9 in Table I, see following report) and an intracochlear schwannoma in a 72-year-old woman (Case 16).

One or more schwannomas were present within the labyrinth in a majority of ears (23 of 26, 88%), occurring within the cochlea, vestibule, or semicircular canals. These intralabyrinthine schwannomas were tumors separate from those in the IAC (multicentric origin) or, less commonly, they were the result of the IAC tumor invading the labyrinth.

Nearly all schwannomas showed high cellularity and were predominantly of the Antoni A variety. Tumors often demonstrated lobular growth patterns with expansion of the IAC and involvement of the labyrinth. It was difficult to pinpoint the nerve of origin of the schwannoma within the IAC in most cases. Bone erosion occurred over a broad front (suggestive of pressure atrophy) or in discrete areas that were sharply demarcated from surrounding healthy bone (suggestive of some other mechanism of osteolysis).

Nearly all cases showed significant degrees of degeneration of sensory and neural elements within the cochlea, such as loss of hair cells, atrophy of the stria vascularis, degeneration of spiral ganglion cells, occurrence of endolymphatic hydrops, and acidophilic staining of the endolymphatic and perilymphatic spaces. Such cochlear pathology occurred in both untreated and treated cases; in the former, the cochlear pathology can be logically attributed as being secondary to the schwannoma.

None of the cases had a history of radiation treatment or pharmacologic therapy for the schwannomas during life. Residual or recurrent schwannomas were seen within the temporal bone in all 17 ears that had undergone surgical resection during life. In these latter cases, the temporal bone tumors were due to the multicentric nature of these neoplasms, occurrence of new schwannomas, or regrowth of residual tumor after surgery.

In some cases, the schwannomas merged with adjacent tumors such as meningiomas, resulting in the formation of "composite" or "fusion" neoplasms. An example is demonstrated in case 3, described later.

Facial nerve involvement by schwannoma was common, occurring in 15 of 26 (58%) of ears. In some cases, the cochleovestibular schwannoma within the IAC invaded the facial nerve directly. In many others, discrete schwannomas arose within various segments of the nerve (see cases 3 and 4).

Three of our cases are described in more detail, as they are representative of our observations.

Case 3

This 43-year-old woman presented at age 19 with progressive left-sided hearing loss and tinnitus. The left-sided hearing loss became profound by age 25, at which time she also developed a mild left facial paresis. A head computed tomography scan revealed bilateral acoustic tumors and multiple meningiomas, resulting in a diagnosis of NF2. The left cochleovestibular schwannoma was successfully resected by a translabyrinthine approach, and the defect was obliterated with abdominal adipose tissue. There was postoperative recovery of facial nerve function. In the ensuing years, she developed multiple intracranial and intraspinal meningiomas and schwannomas, necessitating multiple neurosurgical procedures. She also developed a progressive sensorineural hearing loss in the right ear. At the age of 41, an audiogram showed a downsloping hearing loss on the right, with pure tone average of 37 dB and speech discrimination score of 16%. She died at the age of 43 from brainstem compression due to cerebellar tonsillar herniation. A frame shift mutation in exon 9 (884 del 1bp) was identified in the NF2 gene on chromosome 22q12.2. There was no family history of NF2.

Histologic study of the right ear showed a multicentric cochleovestibular schwannoma (Fig. 1). A large tumor, mainly Antoni type A, completely filled an expanded IAC. Additional schwannomas were present within the scala tympani of the basal turn, the vestibule, and the posterior canal ampulla. There were also separate schwannomas arising within the facial nerve in the labyrinthine, geniculate ganglion, and distal mastoid segments. The cochlea showed partial loss of hair cells, moderate strial atrophy, acidophilic precipitate within both endolymph and perilymph, and near-total degeneration of cochlear neurons. A psammomatous meningioma involving the meninges of the posterior fossa had invaded adjacent mastoid air cells with focal infiltration of the endolymphatic sac. The left ear showed a surgical defect filled with healthy fibrofatty tissue. The distal portion of the IAC showed a composite meningioma-schwannoma neoplasm. The meningioma portion of the neoplasm was characterized by a large number of psammoma bodies with arachnoid-like cells arranged in a whorled appearance. The schwannomatous component of the tumor consisted of spindle-shaped cells in a palisading arrangement. Additional small schwannomas were also present within the scala tympani, the perilymphatic space of the vestibule, and the posterior ampulla. The cochlea showed severe degeneration of sensory and neural structures along with moderate to severe endolymphatic hydrops.

The unoperated (right) ear illustrates the multicentric nature of this neoplasm, with schwannomas arising within the IAC, vestibule, cochlea, posterior canal, and the facial nerve. The histologic findings were typical of many NF2 schwannomas. The IAC was filled and expanded by a highly cellular tumor showing a lobular growth pattern such that the normal cochlear and vestibular nerves could not be identified. The loss of hair cells, neurons and stria within the cochlea along with acidophilic staining of the inner ear fluids was most likely a secondary degenerative phenomenon induced by the tumor. In sporadic tumors, the acidophilic staining has been shown to represent high protein content within the inner ear fluids.[11] The left ear (where tumor had been removed by a translabyrinthine approach) showed a residual and/or recurrent schwannoma within the surgical defect in the distal portion of the IAC where the

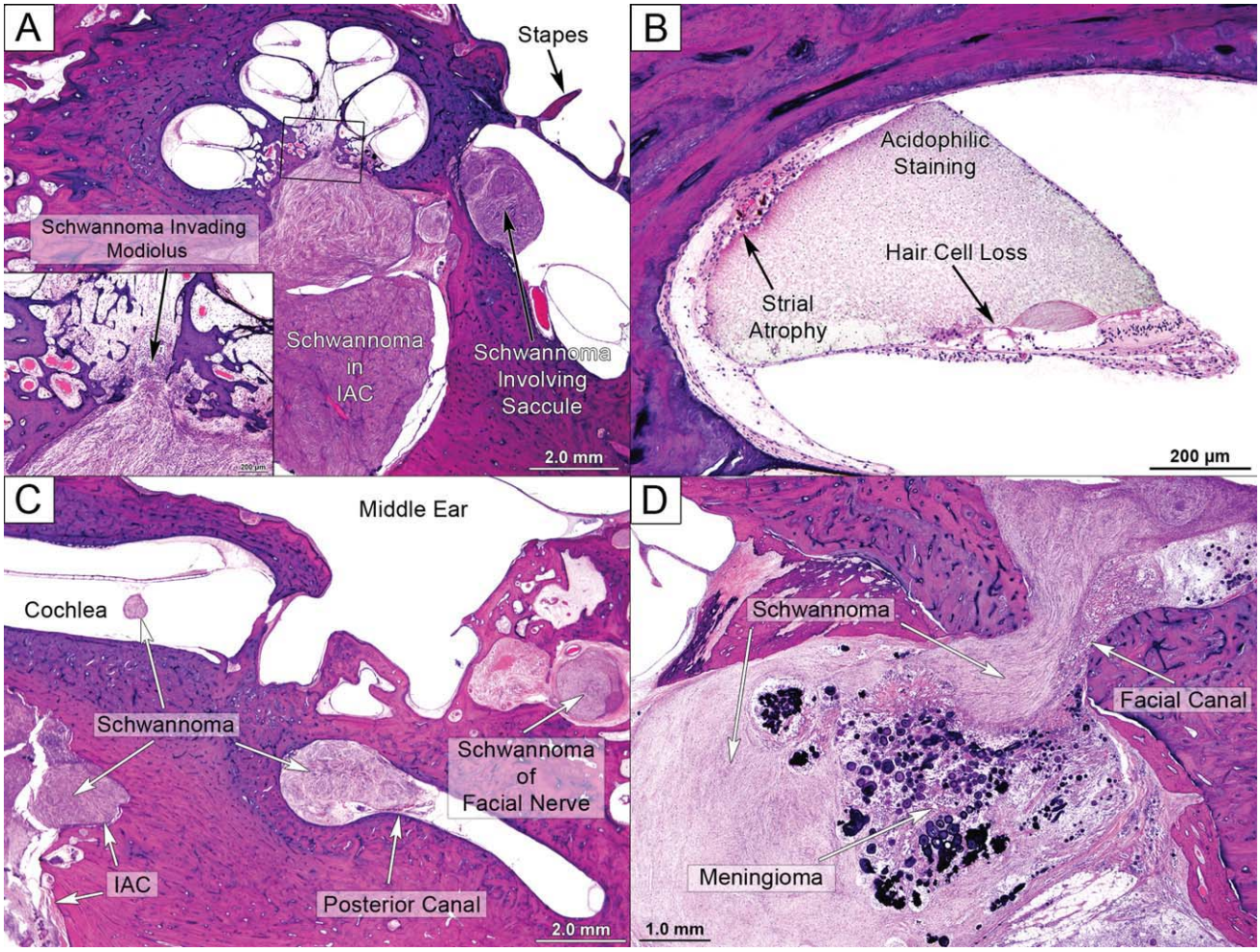

Fig. 1. Case 3, a 43-year-old woman with neurofibromatosis type 2 (NF2) caused by 884del1bp, a frameshift mutation, in exon 9 of the NF2 gene. Photomicrographs shown in (A), (B) and (C) are from the right (untreated) ear, and (D) is from the left ear. (A) There was a large schwannoma, predominantly Antoni type A, that completely filled an expanded internal auditory canal (IAC). Schwannoma also involved the saccule. Inset shows a higher-power view of the cribrose area where schwannoma can be seen invading the modiolus. (B) View of the apical turn of the cochlea demonstrating acidophilic staining of the endolymphatic fluid, moderate atrophy of the stria vascularis, and partial loss of hair cells within the organ of Corti. These degenerative changes in the cochlea were probably caused by the schwannoma and likely contributed to the hearing loss. (C) A section through the basal turn of the cochlea at the level of the round window membrane, demonstrating the multicentric nature of the tumor with separate schwannomas within the IAC, scala tympani, and posterior canal ampulla. There was also a schwannoma arising within the mastoid segment of the facial nerve. (D) Section from left ear that had undergone translabyrinthine resection of the acoustic tumor. The distal portion of the IAC and proximal portion of the facial nerve showed a composite meningioma-schwannoma neoplasm. The meningiomatous component was characterized by a large number of psammoma bodies with arachnoid-like cells arranged in a whorled appearance. The schwannomatous component consisted of spindle-shaped cells in a palisading arrangement.

tumor had fused with an adjoining meningioma to form a composite tumor.

Case 4

This 44-year-old patient developed progressive disequilibrium at age 23 and a hearing loss accompanied by headaches at age 26. Computed tomography scan showed bilateral acoustic tumors and a diagnosis of NF2 was made. At age 27, he underwent two procedures by the suboccipital approach to resect a left cochleovestibular schwannoma, following which he developed bilateral profound hearing loss and left facial nerve paralysis. Because of tumor regrowth, he had another resection of the left-sided schwannoma at age 30. He also underwent two resections of the right-sided tumor at ages 29 and 35. He became quadriplegic and dependent on a ventilator at age 35. Tracheostomy and gastrostomy tube placements were performed. He developed progressive renal failure as a result of pyelonephritis and died at the age of 44. There was a family history of NF2; his father, brother, and son were all affected. A nonsense mutation in exon 11 (C1021T, Arg341X) was identified in the NF2 gene. Autopsy revealed bilateral cochleovestibular schwannomas, schwannomas involving multiple spinal roots and peripheral nerves as well as the intramedullary spinal cord, multiple meningiomas, and cortical glial hamartomas. Only the left temporal bone was available for study.

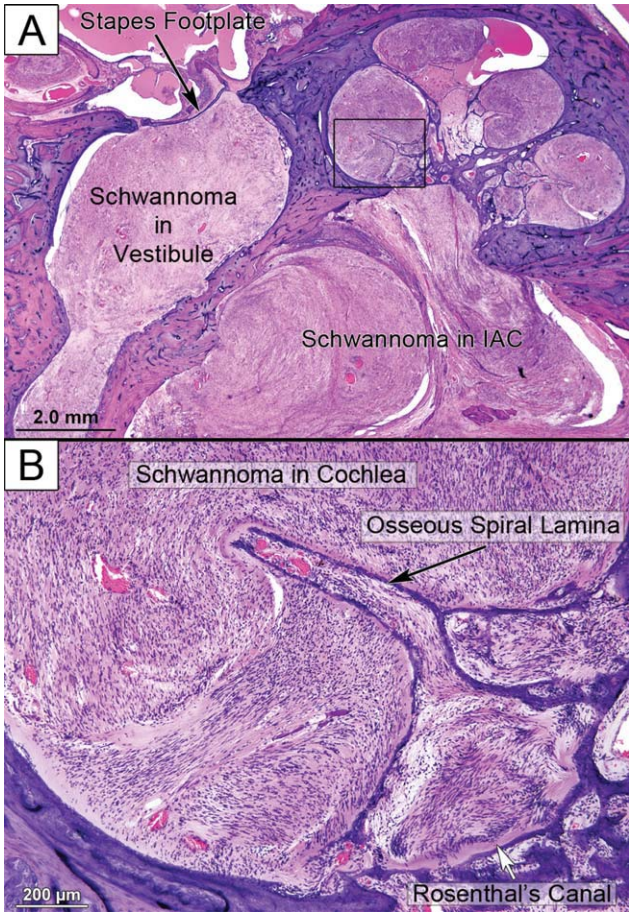

Fig. 2. Case 4, a 44-year-old man with neurofibromatosis type 2 (NF2) due to C1021T, Arg341X nonsense mutation in exon 11 of the NF2 gene. (A) Schwannoma filled an expanded internal auditory canal and inner ear spaces. The tumor was highly cellular, demonstrating a predominantly Antoni type A pattern. The vestibule was completely filled with tumor; no remnants of the utricle or saccule could be ascertained. The anterior part of the footplate and annular ligament were pushed outwards by the neoplasm. (B) A higher-power view of the basal turn of the cochlea demonstrating that the schwannoma completely filled the fluid spaces with replacement of all cochlear sensory structures. Schwannoma had also invaded Rosenthal's canal and the osseous spiral lamina. IAC = internal auditory canal.

The IAC and nearly the entire bony labyrinth were filled by a large, multilobulated schwannoma that consisted almost entirely of Antoni type A cells (Fig. 2). Verocay bodies, which are arrangements of nuclei and fibers that resemble tactile corpuscles, were present in many areas. Some areas of the tumor showed multiple, dilated, thin-walled blood vessels, devoid of musculature in the vessel wall. The schwannoma had replaced all sensory and neural structures of the inner ear. Tumor filled the basal and middle turns of the cochlea, and the apical turn contained eosinophilic-staining fluid. Tumor also filled the basal turn of Rosenthal's canal, while the remainder of the canal showed degeneration of nearly all spiral ganglion cells. The bony vestibule was filled by schwannoma, which caused outward displacement of the anterior part of the annular ligament along with bowing of the stapes footplate. Schwannoma also filled the ampullated ends of the three semicircular canals. The labyrinthine portion of the facial nerve was replaced by schwannoma. Discrete foci of schwannoma were also seen arising within the tympanic and mastoid segments of the nerve with degeneration of the surrounding nerve fibers.

This case illustrates the aggressive behavior of NF2 schwannomas with multicentric origin, presence of extralabyrinthine and intralabyrinthine schwannoma, and tendency for recurrence after surgery. It also demonstrates the involvement of the facial nerve by schwannoma because of a combination of the acoustic tumor invading the nerve as well as schwannoma arising with the facial nerve itself.

Case 9

This 89-year-old patient presented at the age of 68, with a complaint of a bilateral progressive hearing loss of 14 years' duration. There was also tinnitus in her left ear. There was a history of hearing loss in her sister. She was in good health except for myasthenia gravis. An audiogram at age 68 showed a bilateral downsloping mixed hearing loss with speech-reception threshold of 65 dB on the right, 70 dB on the left, and speech discrimination scores of 52% (right) and 57% (left). She underwent successful stapedectomy procedures, first on the right, and then on the left using a Gelfoam wire prosthesis. Serial audiograms showed a progressive sensorineural hearing loss in the ensuing years with loss in discrimination, particularly in the right ear. She died at the age of 89.

The right ear showed a schwannoma occupying the distal three quarters Rosenthal's canal, with loss of nearly all cochlear neurons innervating the upper basal, middle, and apical turns (Fig. 3). The schwannoma did not invade the cochlear fluid spaces or the IAC. The IAC contained the cochlear and vestibular nerves, both of which appeared normal, including Scarpa's ganglion. The organ of Corti was missing in the basal turn and showed partial loss of outer hair cells in the remaining turns. There was moderate patchy atrophy of stria vascularis. There was no endolymphatic hydrops. The vestibular end organs were normal for age. The facial canal and nerve were normal. The otic capsule showed a focus of otosclerosis anterior to the oval window; the focus did not reach the cochlea. A total stapedectomy had been done with connective tissue bridging the oval window. The left ear was similar in appearance to the right; the schwannoma within the Rosenthal's canal was smaller than in the contralateral ear.

This case illustrates that NF2 can have an indolent course. Although the schwannoma likely contributed to this patient's hearing loss, it did not result in any significant morbidity, and the patient had a normal life span. Similar examples include Case 5 (male, aged 70 years), Case 8 (male, aged 70 years) and Case 16 (female, aged 72 years).

DISCUSSION

Investigators have described temporal bone findings in patients with sporadic (unilateral) cochleovestibular schwannomas.[6,7,12,13] Typically, these neoplasms are

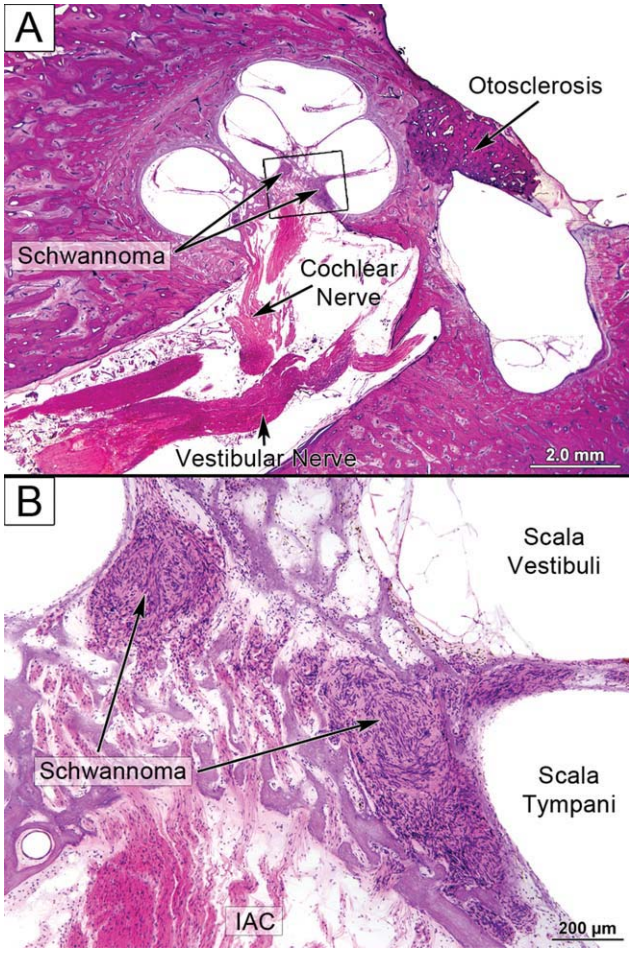

Fig. 3. Case 16, an 89-year-old woman with neurofibromatosis type 2 manifesting as bilateral cochlear schwannomas and an indolent course. (A) Low-power view showing cochlea, internal auditory canal (IAC), and otic capsule. There was a small schwannoma within the cochlear modiolus. The cochlear and vestibular nerves within the IAC appeared normal. There was a focus of otosclerosis anterior to the oval window. (B) A higher power view of the modiolus showing the schwannoma replacing nearly all of the cochlear neurons innervating the upper basal and middle turns. The schwannoma had not invaded the cochlear fluid spaces or the IAC.

located within the IAC and consist of a single tumor. Histologic subtypes include Antoni type A (compact tissue of schwannoma cells) and Antoni type B patterns (a degenerate form characterized by fatty or hyaline degeneration and reduced cellular content). Growth rates may vary, and many tumors become dormant after an initial period of growth.[7]

The present study shows clear differences in the biologic behavior of cochleovestibular schwannoma in NF2 compared to sporadic cases. The majority of cases in our series had large intra- and extralabyrinthine schwannomas with multicentric origin; further, most of the tumors were Antoni type A. Our study also showed that the majority of these schwannomas were aggressive, often involving the labyrinth, including the cochlea and vestibular end organs. In some cases, the schwannomas merged with adjacent tumors such as meningiomas, resulting in the formation of composite or fusion neoplasms. These findings underscore the surgical challenge posed by NF2 tumors in accomplishing successful total removal and long-term control.

There were similarities between our findings, utilizing histology of the entire temporal bone, and the observations of Sobel,[14] who examined the histologic features of cochleovestibular schwannomas obtained at the time of surgical resection from patients with NF2 (48 specimens) and unilateral, non-NF2 cases (293 specimens). Sobel reported that Antoni A and B areas, nuclear atypia, whorls, scarring, and chronic inflammation were found equally in both sporadic and NF2 groups. NF2 schwannomas had more Verocay bodies, foci of high cellularity and lobular growth pattern. Unilateral schwannomas showed more hyalinized and malformed vessels, recent and old thromboses, and hemosiderin deposits. NF2 tumors also showed fusion neoplasms, which were not seen in sporadic cases.

Our findings also suggest that long-term preservation of hearing would be more challenging than with unilateral acoustic tumors for a number of reasons. One reason is that NF2 schwannomas may infiltrate between fibers of the cochlear nerve, making it difficult to preserve functioning axons at the time of surgical resection.[8,9] In addition, NF2 patients are at risk for progressive or delayed hearing loss after initial successful hearing preservation because new schwannomas may arise, as these tumors are often multicentric. Secondary degenerative changes in the cochlea caused by these tumors also undoubtedly contribute to the hearing loss. As targeted molecular therapies are developed in the future to combat the growth of these tumors with the goal of preservation of hearing,[15,16] the new therapies will have to not only control the tumor growth but also will have to prevent or reverse the secondary degenerative changes within the cochlea caused by these tumors.

CONCLUSIONS

Involvement of the temporal bone in NF2 typically consists of multicentric schwannomas involving the internal auditory canal as well as locations within the labyrinth. The schwannomas are predominantly cellular (Antoni type A) and, in general, they show aggressive behavior, often involving the labyrinth. There is often secondary degeneration within the cochlear and vestibular organs. In some cases, schwannomas may fuse with adjacent tumors such as meningiomas, resulting in the formation of composite or fusion neoplasms. Thus, total removal and removal of tumors with preservation of hearing are more difficult than with sporadic unilateral cochleovestibular schwannoma.

Acknowledgment

We thank Jon Pack for the photomicrographs.

BIBLIOGRAPHY

1. Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet* 2009;373:1974–1986.
2. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. *Orphanet J Rare Dis* 2009;4:16.

3. Benitez JT, Lopez-Rios G, Novoa V. Bilateral acoustic neuroma. A human temporal bone report. *Arch Otolaryngol* 1967;86:25–31.
4. DeMoura LF, Hayden RC Jr, Conner GH. Bilateral acoustic neurinoma and neurofibromatosis. *Arch Otolaryngol* 1969;90:28–34.
5. Flexon PB, Nadol JB Jr, Schuknecht HF, Montgomery WW, Martuza RL. Bilateral acoustic neurofibromatosis (neurofibromatosis 2): a disorder distinct from von Recklinghausen's neurofibromatosis (neurofibromatosis 1). *Ann Otol Rhinol Laryngol* 1991;100:830–834.
6. Nager GT. Acoustic schwannomas. In: *Pathology of the Ear and Temporal Bone*. Nager GT, Hyams VJ, eds. Baltimore, MD: Williams and Wilkins; 1993:515–567.
7. Merchant SN, McKenna MJ. Neoplastic growth. In: *Schuknecht's Pathology of the Ear*, 3rd Ed. Merchant SN, Nadol JB Jr, eds. Shelton, CT: PMPH-USA Inc., 2010; 477–536.
8. Linthicum FH Jr. Unusual audiometric and histologic findings in bilateral acoustic neurinomas. *Ann Otol Rhinol Laryngol* 1972;81: 433–437.
9. Linthicum FH Jr, Brackmann DE. Bilateral acoustic tumors. A diagnostic and surgical challenge. *Arch Otolaryngol* 1980;106:729–733.
10. Merchant SN. Methods of removal, preparation and study. In: *Schuknecht's Pathology of the Ear*, 3rd Ed. Merchant SN, Nadol JB Jr, eds. Shelton, CT: PMPH-USA Inc; 2010:3–51.
11. Silverstein H, Schuknecht HF. Biochemical studies of inner ear fluid in man. Changes in otosclerosis, Meniere's disease, and acoustic neuroma. *Arch Otolaryngol* 1966;84:395–402.
12. Eckermeier L, Pirsig W, Mueller D. Histopathology of 30 non-operated acoustic schwannomas. *Arch Otorhinolaryngol* 1979;222:1–9.
13. Mahmud MR, Khan AM, Nadol JB Jr. Histopathology of the inner ear in unoperated acoustic neuroma. *Ann Otol Rhinol Laryngol* 2003;112:979–986.
14. Sobel RA. Vestibular (acoustic) schwannomas: histologic features in neurofibromatosis 2 and in unilateral cases. *J Neuropathol Exp Neurol* 1993; 52:106–113.
15. Plotkin SR, Singh MA, O'Donnell CC, Harris GJ, McClatchey AI, Halpin C. Audiologic and radiographic response of NF2-related vestibular schwannoma to erlotinib therapy. *Nat Clin Pract Oncol* 2008;5:487–491.
16. Plotkin SR, Halpin C, McKenna MJ, Loeffler JS, Batchelor TT, Barker FG 2nd. Erlotinib for progressive vestibular schwannoma in neurofibromatosis 2 patients. *Otol Neurotol* 2010;31:1135–1143.