

BRIEF REPORT

Tumors of the Endolymphatic Sac in von Hippel–Lindau Disease

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TUMORS OF THE ENDOLYMPHATIC SAC ARE LOCALLY INVASIVE NEOPLASMS arising in the temporal bone that can cause hearing loss, tinnitus, vertigo, aural fullness, and facial-nerve dysfunction. They occur sporadically but are most often associated with von Hippel–Lindau disease; in such instances, they are frequently bilateral. The natural history, mechanisms underlying the early symptoms, anatomical origin of endolymphatic-sac tumors, and optimal timing of their treatment are unknown.

We describe three cases of von Hippel–Lindau disease that illustrate the following features of endolymphatic-sac tumors: morbid hearing loss due to a radiologically undetectable microscopic tumor in the endolymphatic sac or duct; initial symptoms that are caused by hemorrhage, endolymphatic hydrops, or both; an origin in the endolymphatic duct or sac; and molecular evidence of an association with von Hippel–Lindau disease. Early detection of endolymphatic-sac tumors, which permits their resection in patients who can still hear, may reduce the incidence and severity of neurologic dysfunction that is associated with these tumors.

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 CASE REPORTS

PATIENT 1

A 40-year-old man had received a diagnosis of von Hippel–Lindau disease in 1973, after resection of a cerebellar hemangioblastoma. In 1982, he noted tinnitus, vertigo, and hearing loss in the right ear, followed by progressive hearing loss in the left ear. Meniere's disease was diagnosed, and the patient underwent fenestration of the right inner ear in 1985 and the left in 1987, but without relief of symptoms. In 1993, he underwent bilateral nephrectomy for renal carcinoma and a right adrenalectomy for pheochromocytoma. He was then referred to the National Institutes of Health (NIH) because of continued vertigo, bilateral tinnitus, and profound bilateral hearing loss. Magnetic resonance imaging (MRI) revealed an abnormality in the right, but not the left, temporal region (Fig. 1A). A computed tomographic (CT) study showed erosion of the bone adjacent to the right endolymphatic sac. Five weeks later, the patient died. His temporal bones were removed at autopsy (Fig. 1B through 1F).

PATIENT 2

A 43-year-old man had received a diagnosis of von Hippel–Lindau disease in 1981. He underwent a left nephrectomy in 1984 and a right partial nephrectomy in 1997 for renal-cell carcinoma. Cerebellar hemangioblastomas were treated in 1994, 1997, and 1999. In 1999, he had attacks of vertigo and tinnitus in the left ear. An MRI scan of the temporal bones was unremarkable. Pancreatic neuroendocrine tumors were treated in 2000. In 2002, he had progressive hearing loss in the left ear and was referred to the NIH. At that time, he reported worsening vertigo, tinnitus in the left ear, and hearing

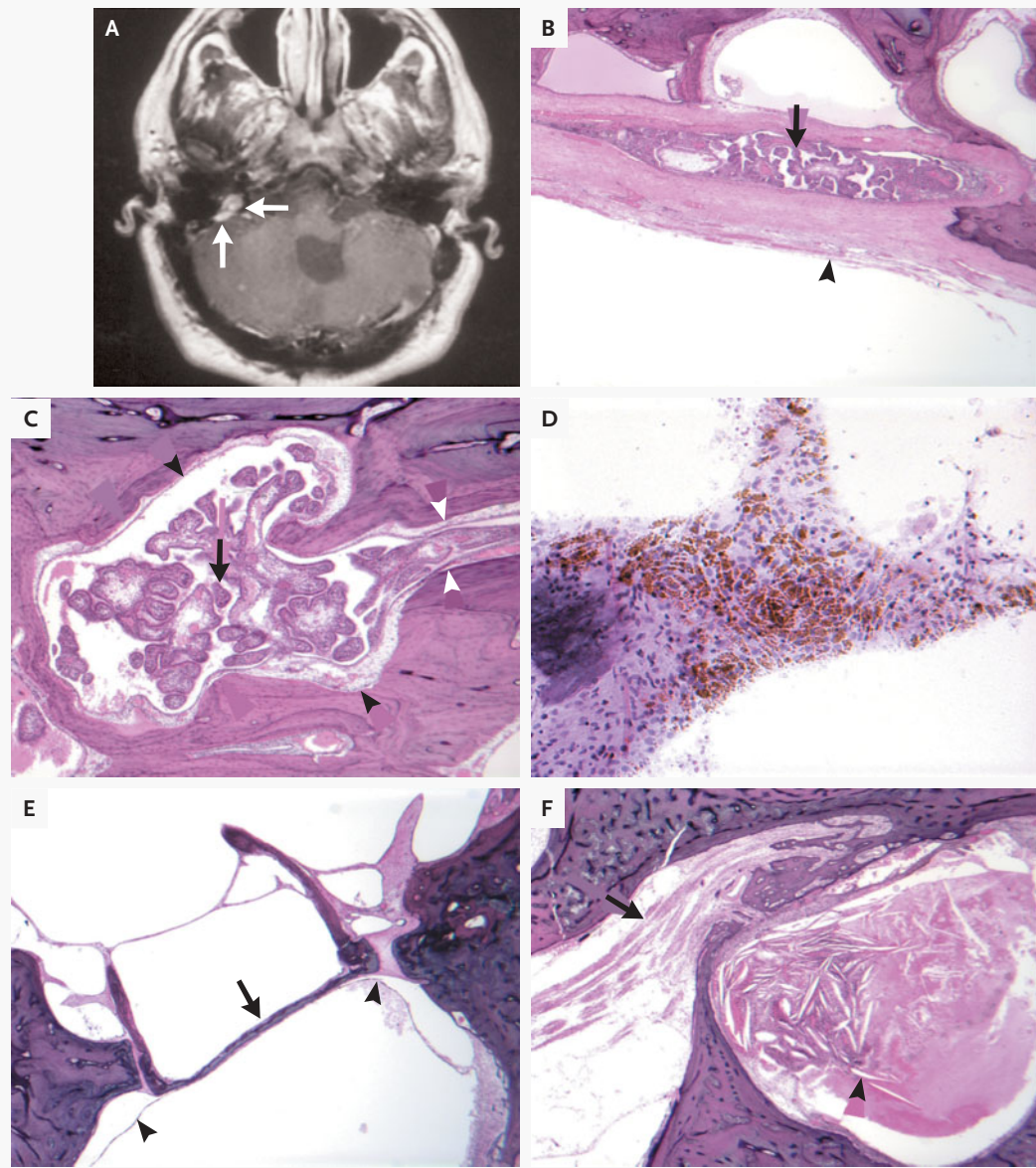


Figure 1. MRI Scan and Histologic Analyses of the Temporal Bones in Patient 1.

The axial T₁-weighted, contrast-enhanced MRI scan in Panel A reveals an enhancing endolymphatic-sac tumor in the right temporal bone (arrows). Despite the patient's bilateral hearing loss, no abnormality was evident in the left temporal region. Sections of temporal bone show papillary tumors in both endolymphatic sacs. As Panel B (hematoxylin and eosin, ×5) shows, the left endolymphatic-sac tumor (arrow) extends from the endolymphatic duct into the endolymphatic sac, which is contained within the posterior fossa dura (arrowhead). In Panel C (hematoxylin and eosin, ×20), the endolymphatic-sac tumor in the left temporal bone (arrow) is within the duct (white arrowheads) and has eroded the contiguous region (black arrowheads). Panel D (hematoxylin and eosin, ×40) shows the intralabyrinthine reactive response in the inner ear along with cells containing deposits of hemosiderin (brown staining) within the vestibule in the region of the macula utriculi. In Panel E (hematoxylin and eosin, ×10), distention of the saccular membrane indicates endolymphatic hydrops. The distended sacculle (arrowheads) adheres to the undersurface of the footplate of the stapes (arrow). Panel F (hematoxylin and eosin, ×5) shows neuronal degeneration (arrow) of the superior division of the vestibular nerve. Reactive changes, including cholesterol clefts (arrowhead), are evident in the vestibule adjacent to the macula utriculi.

loss. An audiogram revealed moderate (low-frequency) to severe (high-frequency) sensorineural hearing loss in the left ear. An MRI scan showed enhancement of the endolymphatic sac and intralabyrinthine hemorrhage in the left ear. A CT scan revealed minimal bone erosion adjacent to the left endolymphatic sac. At surgery, a small endolymphatic-sac tumor associated with hemorrhage was apparent when the endolymphatic duct and sac were opened. The duct and sac were resected with the tumor. The tinnitus and vertigo resolved after surgery, and the findings on a postoperative audiogram were similar to those on the preoperative audiogram.

PATIENT 3

The third patient was a 34-year-old woman with von Hippel–Lindau disease in whom tinnitus of the left ear had developed in 2000. An MRI scan of the temporal bones was unremarkable (Fig. 2A). In 2002, she reported vertigo and acute hearing loss in the left ear. An MRI scan showed left intralabyrinthine hemorrhage but no tumor (Fig. 2B). In 2003, on referral to the NIH, the patient reported acute hearing loss in the left ear during the previous month and worsening tinnitus and vertigo. An audiogram revealed sensorineural hearing loss that was mild (low frequency) to severe (high frequency). MRI scans revealed intralabyrinthine hemorrhage and a 3-mm enhancing lesion in the endolymphatic duct (Fig. 2C and 2D). A CT scan revealed bone erosion adjacent to the duct (Fig. 2E). At surgery, a small endolymphatic-sac tumor originating from the endolymphatic duct and invading the adjacent temporal bone was removed. The tinnitus and vertigo resolved after surgery, and the findings on a postoperative audiogram were similar to those on the preoperative audiogram.

METHODS

TEMPORAL BONES

After decalcification, the temporal bones of Patient 1 were cut into axial sections that were 20 μ m thick.

TUMORS

Tumors were studied with the use of routine staining and immunohistochemical evaluation for glial fibrillary acid protein, vimentin, epithelial membrane antigen, cytokeratin, CD34, and MAK-6. Genetic testing confirmed a germ-line mutation in the von Hippel–Lindau (*VHL*) gene in Patients 2 and 3,

whose endolymphatic-sac tumors were analyzed by fluorescence in situ hybridization (FISH).¹ Chromosomes prepared from peripheral-blood lymphocytes in metaphase from the two patients were stained with 5-bromo-2'-deoxyuridine and used as a template. FISH was performed as described elsewhere.²

RESULTS

HISTOLOGIC FEATURES OF THE TEMPORAL BONES

Each temporal bone from Patient 1 contained an endolymphatic-sac tumor. The large tumor of the right temporal bone had typical histologic features, including cuboidal tumor cells forming papillotubular structures, erosion into the surrounding mastoid air cells, and an extensive inflammatory response within the mastoid air cells and labyrinth. The left temporal bone contained papillary-cell proliferation in a microscopic tumor along the endolymphatic duct, an intralabyrinthine inflammatory response, and hemosiderin within the vestibule in the region of the macula utriculi. Bilateral neuronal degeneration of the superior division of the vestibular nerve was evident. Bilateral endolymphatic hydrops was present (Fig. 1E).

ANALYSIS OF SURGICAL SPECIMENS

The resected tumors from Patients 2 and 3 had the histologic features of endolymphatic-sac tumors. The cells stained for cytokeratin, vimentin, epithelial membrane antigen, CD34, and MAK-6, but not for glial fibrillary acid protein. FISH analysis revealed deletion of the wild-type allele in tumor cells, confirming the loss of heterozygosity, but retention of the wild-type allele in surrounding normal tissues (Fig. 3).

DISCUSSION

The prevalence of von Hippel–Lindau disease, an autosomal dominant syndrome resulting from a germ-line mutation in the *VHL* gene on chromosome 3,³ is approximately 1 per 39,000 people.⁴ The syndrome includes renal cysts and renal carcinoma, pheochromocytoma, pancreatic cysts, neuroendocrine tumors, cystadenomas of the reproductive adnexal organs, and hemangioblastomas of the cerebellum, spinal cord, brain stem, and retina.⁵

Despite descriptions of petrous-bone lesions by Brandt⁶ and Lindau⁷ in the 1920s and sporadic reports of endolymphatic-sac tumors in patients

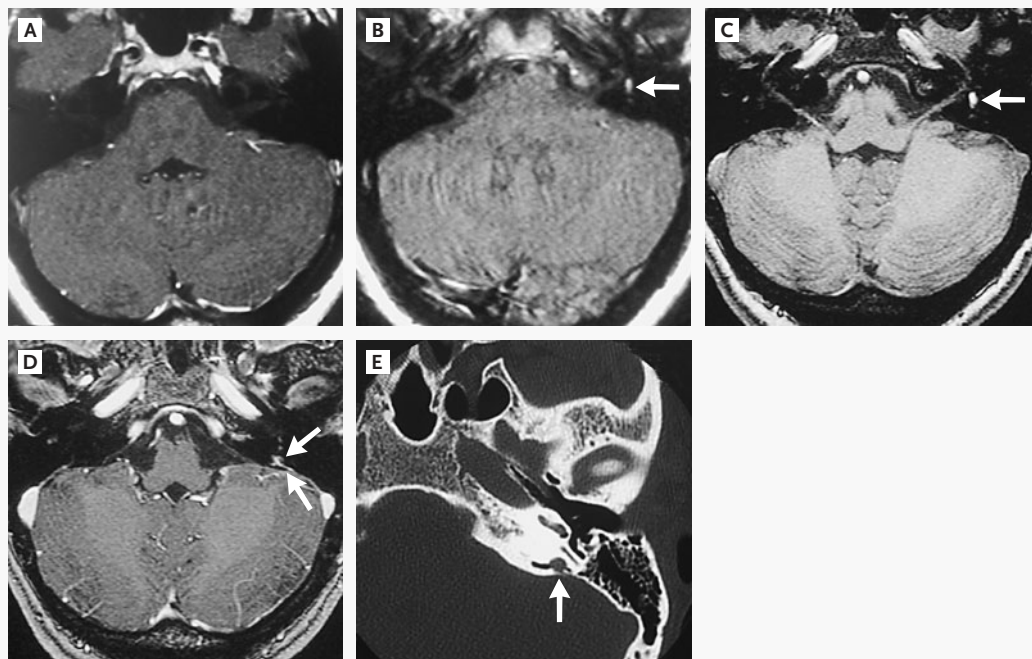


Figure 2. MRI and CT Scans of the Temporal Region in Patient 3.

Panels A through D show axial T₁-weighted, MRI scans. Panel A shows a contrast-enhanced scan from 2000 with no evidence of an endolymphatic-sac tumor, despite the patient's report of left tinnitus. By 2002, worsening tinnitus, acute hearing loss in the left ear, and vertigo had developed. Panel B shows a non-contrast-enhanced scan that reveals left intralabyrinthine hemorrhage (arrow) but no evidence of an enhancing tumor. In 2003, mild-to-severe hearing loss developed in the left ear of the patient while she continued to have left tinnitus and vertigo. Panel C shows a non-contrast-enhanced scan with evidence of intralabyrinthine hemorrhage (arrow), and Panel D shows a contrast-enhanced scan with enhancement in the region of the left endolymphatic duct (arrows) — findings that are consistent with the presence of an endolymphatic-sac tumor. Panel E shows an axial, non-contrast-enhanced CT scan that reveals a bony erosion in the region of the left endolymphatic duct (arrow).

with von Hippel–Lindau disease, such tumors were not formally recognized as part of von Hippel–Lindau disease until the late 1990s.⁸ These tumors rarely occur in people who do not have von Hippel–Lindau disease. They are detected by MRI or CT in 11 to 16 percent of patients with the disease.^{8,9} Bilateral tumors occur in 30 percent of patients with von Hippel–Lindau disease who have endolymphatic-sac tumors.^{8,10}

Of those patients with von Hippel–Lindau disease who have evidence on imaging of an endolymphatic-sac tumor, 95 percent have hearing loss, 92 percent have tinnitus, 62 percent have vertigo or disequilibrium, 29 percent have aural fullness, and 8 percent have facial paresis — symptoms that are all attributable to the lesion.^{8,9} Hearing loss is acute and clinically significant in 43 percent of patients and occurs in a stepwise, progressive manner over a

period of three to six months in another 43 percent; 14 percent of patients have gradual hearing loss.⁹ Typically, the loss is irreversible⁹ and occurs early in life (mean age at onset, 22 years).⁸ It usually coincides with the peak of vestibular symptoms,⁹ as it did in the patients described here.

In almost 60 percent of patients with von Hippel–Lindau disease who have vestibulocochlear symptoms, there is no evidence on imaging of an endolymphatic-sac tumor.⁸ The cause of these symptoms is unknown, but our descriptions of the three patients suggest that the symptoms can be due to a microscopic tumor.

Previous investigators have concluded that hearing loss associated with endolymphatic-sac tumors results from invasion of inner-ear structures such as the semicircular canal or cochlea.⁹ In our patients, who did not have findings on imaging or operative

or histologic evidence of invasive tumors in these structures, the mechanism of hearing loss and vestibular symptoms was probably intralabyrinthine hemorrhage, hydrops formation related to the tumor, or both.

Acute intralabyrinthine hemorrhage may explain the irreversible, acute, and clinically significant hearing loss that often occurs in patients with an endolymphatic-sac tumor, as shown in Figure 2.^{8,9,11} The irreversibility of symptoms (particularly hearing loss) may result from cochlear and neuronal degeneration (as observed in Patient 1) after hemorrhage or secondary inflammation.

Hydrops (Fig. 1E) may explain the Meniere's-like clinical syndrome (hearing loss, tinnitus, and vertigo) in patients with an endolymphatic-sac tumor.^{8,9} Hydrops may result from blockage of the reabsorption of endolymph in the endolymphatic sac, inflammation in response to hemorrhage, or excessive production of fluid by the tumor. The production of peritumoral fluid by the tumor is analogous to the development of peritumoral edema and the formation of cysts — occurrences that are frequently associated with central nervous system hemangioblastomas^{12,13} and visceral tumors in cases of von Hippel–Lindau disease.⁵

The origin of endolymphatic-sac tumors has been debated since their classification as a unique histologic entity by Heffner.¹⁴ Sites other than the endolymphatic sac, such as the middle ear and mastoid air cells, have been proposed. Confusion regarding the origin of the tumors is probably due to previous descriptions of large tumors that encompassed substantial portions of the temporal bone, making it impossible to determine the exact anatomical origin. All the microscopic endolymphatic-sac tumors that we describe originated in the endolymphatic duct or sac. Furthermore, FISH analysis showed that the tumors were localized to these structures. These findings confirm the proposals by Heffner¹⁴ and Megerian et al.¹⁵ that endolymphatic-sac tumors originate in the endolymphatic sac.

Genetic analysis of the two tumors that were surgically resected revealed germ-line mutations combined with deletion of the wild-type *VHL* allele, findings that support the clinical⁸ and genetic¹⁶ association of endolymphatic-sac tumors with von Hippel–Lindau disease and the molecular sequence of events postulated by Knudson.¹⁷ Inactivation of both alleles of the *VHL* gene occurs in other tumors associated with von Hippel–Lindau disease, such as hemangioblastomas, renal-cell carcinomas, pheo-



Figure 3. Fluorescence in Situ Hybridization Analysis of Cells from the Endolymphatic-Sac Tumor and Surrounding Normal Tissue in Patient 3.

Only one pink signal, which represents the *VHL* gene, is seen in each of the two tumor cells, indicating loss of heterozygosity in the tumor. Two pink signals are evident in the normal surrounding tissue, indicating maintenance of the wild-type allele ($\times 150$).

chromocytomas, and pancreatic neuroendocrine tumors.⁵

Complete surgical resection of the endolymphatic-sac tumors is curative and can be performed with the preservation of hearing and the alleviation of vestibular symptoms. Because of the sudden, clinically significant, and irreversible hearing loss associated with the tumor, early surgical intervention is important to prevent permanent neurologic symptoms and deficits. Therefore, early diagnosis on the basis of serial clinical evaluations and high-resolution imaging to detect small tumors or intralabyrinthine hemorrhage is warranted. Advances in imaging techniques may also improve our ability to detect these tumors early.

Patients who have a visible tumor but who can still hear require surgery to prevent neurologic decline. Deaf patients with evidence on imaging of a tumor should undergo resection if other neurologic symptoms are present. It remains to be determined whether patients with clinical symptoms of endolymphatic-sac tumors, but without evidence of a tumor or hemorrhage on imaging, should undergo exploratory surgery to prevent hearing loss or to alleviate symptoms.

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