Origin of Endolymphatic Sac Tumor

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Abstract Autopsy temporal bone sections showing a one mm papillary glandular neoplasm, confined to the left endolymphatic duct, are described. This is the second literature report confirming the post-mortem site of origin of the “endolymphatic sac tumor”. The patient died after surgery for right vestibular schwannoma, but no features of von Hippel Lindau disease or neurofibromatosis 2 had been displayed clinically or at autopsy. A study of the epithelium of *normal* human mature endolymphatic ducts and sacs (EDSs) in archival temporal bone sections showed hyperplastic tubular outgrowths, usually situated in the intraosseous portion of the endolymphatic sac, in most cases. Such appearances imply that the epithelium of the EDS has the potential of producing a malignant papillary glandular neoplasm. Papillary ingrowths, some forming collagenous polypoid projections, and cysts were frequent among the epithelial cells. Psammoma bodies were present in the ducts and sacs of older patients. Appearances suggesting erosion of the bony interface of vestibular aqueduct with EDS could be ascribed to the entry and exit of blood vessels into and from the vestibular aqueduct. Care should be taken in the evaluation of surgical or autopsy material from EDSs not to overcall any of these normal features as malignant.

Keywords Endolymphatic sac/duct tumor · Autopsy · von Hippel Lindau disease · Vestibular schwannoma

Introduction

The endolymphatic *duct* arises in the posteroinferior part of the vestibule of the inner ear as the result of the union of an endolymph-containing epithelial tube from the saccule and one from the utricle. This tube passes into a bony canal, the vestibular aqueduct, and extends posteriorly and laterally. It soon widens in a superior-inferior plane but not in an anteroposterior one, and is here known as the endolymphatic *sac* (Fig. 1). The sac then extends to the outside of the temporal bone, at first bordered medially by a wide mound of bone, the medial lip, and then lying in soft tissue between two layers of dura, and ending here blindly on the posterior wall of the temporal bone. The anatomical position of the junction of duct with sac has not been well-defined. The function of the endolymphatic duct and sac (EDS) is still not certain. It had been reputed to be associated with resorption of endolymph, but modern scientific opinion is now veering in the direction of regarding it as the locus of endolymph volume regulation [1].

Pathological changes in the EDS were, until recently, considered rare and arcane. A marked dilatation of those structures associated with hearing loss and Pendred syndrome was well substantiated, but obstructive changes reputedly related to hydrops of the endolymphatic system and Ménière’s disease were poorly verified. The description of a new pathological entity of the endolymphatic sac by Heffner came quite unexpectedly in 1989. This was an epithelial neoplasm which he surmised to arise in the endolymphatic sac [2]. Heffner’s 20 cases showed papillary cystic and glandular patterns. All were diagnosed during life. In each there was extensive infiltrative growth leading to Heffner’s designation of these neoplasms as “adenocarcinomas”, a concept that he subsequently retracted. None had been studied at autopsy. Heffner,

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Fig. 1 3-D model of membranous labyrinth (red) with the endolymphatic duct and sac, which have been recolored in green. The model has been rotated to show the endolymphatic duct and sac in the foreground. ES: endolymphatic sac; ED: endolymphatic duct; S: sacculle; U: utricle; PSC: posterior semicircular canal; LSC: lateral semicircular canal; SSC: superior semicircular canal; BC: basal coil of cochlea. The narrow indentations and slits in the endolymphatic sac are caused by prominent blood vessels entering or leaving that structure. The small gap in the narrow duct (ductus reuniens) between the basal coil of the cochlea and the sacculle is an artefact produced by the angle of view of the model. Reproduced and adapted by kind permission of Dr Saumil Merchant from the 3-D model of a human temporal bone prepared from a 14-year-old male using archival 20 μ m thick histological sections. Available from: <https://research.meei.harvard.edu/otopathology/3dmodels/3dviewer.html> Accessed March 24, 2007

however, formulated the concept that the endolymphatic sac was the source of the neoplasm primarily by evaluation of the imaging of the temporal bones taken during life in which he found that the centers of the tumor masses tended to be at or near the posterior medial face of the petrous bone. He also compared the light microscopic features, immunohistochemical staining pattern and ultrastructural findings of nonneoplastic endolymphatic sac epithelium to the epithelial cells of the endolymphatic sac papillary tumor showing similarities in histology, immunostaining characteristics and ultrastructure, thereby, leading to the same conclusions.

Recent experience has supported Heffner's shrewd concept of a papillary glandular neoplasm arising in the endolymphatic duct/sac region. It has been recognized that this neoplasm is one of a group of mainly malignant ones occurring in the familial condition of von Hippel Lindau disease [3, 4]. In some cases with that disease

endolymphatic sac tumor has been diagnosed by imaging to be arising in the EDS region and causing local bone erosion, and this diagnosis has been followed by successfully surgical excision [5].

In a review of archival temporal bone sections we found an early endolymphatic tumor—in fact arising in the endolymphatic duct—on the side contralateral to a large vestibular schwannoma, in a patient who died in 1961. Both temporal bones had been removed at autopsy from this patient and processed serially for histology, so it was possible to study the neoplasm in situ at this early stage of its development.

Clinical Presentation

The patient was a 61 year-old lady. She complained of severe right-sided sensorineural hearing loss, chiefly affecting higher frequencies. On examination there was ataxia of gait and stance and spontaneous vestibular nystagmus. Caloric responses showed a severe reduction on the right; responses were present on the left, but with directional preponderance to the left. A clinical diagnosis of vestibular schwannoma was confirmed on radiology. A large right-sided vestibular schwannoma was removed at operation, but the patient died 48 hours later.

Autopsy

Clotted blood was found in the cerebellopontine angle in relation to right anteroinferior cerebellar artery and there was occlusion of small branch of the right anteroinferior cerebellar artery by thrombus. The right cerebellar hemisphere and right middle cerebral peduncle were very soft and friable. A necrotic area was found on left side of the pons extending to the midbrain. Histological examination showed infarcted brain tissue. There was no evidence of neoplasia in any part of the brain tissue. Except for some small fibromyomata of the uterus there was no evidence of neoplasia in any other organ.

Material and Methods

Both temporal bones had been removed at the autopsy, trimmed, fixed in formaldehyde solution, processed and embedded in low viscosity nitrocellulose (LVN), a substance with properties similar to that of celloidin. Such substances are used to embed temporal bones for microtomy in preference to paraffin wax because of the superior preservation of tissue architecture. Unlike the situation with paraffin wax, immunohistochemical or other

molecular investigations can be performed only with difficulty on tissues embedded in these materials. Sections had been cut horizontally (axially) at 20 μm thickness throughout both temporal bones. Every tenth section had been then stained with hematoxylin and eosin and mounted on a glass slide.

In addition, in order to attempt to throw light on the tissue of origin of endolymphatic sac tumor and also to interpret the significance of several structures that were found near the endolymphatic duct tumor in the left temporal bone of propositus, the normal EDSs were studied in temporal bones in which the endolymphatic structures were free from pathological changes.

Microscopic Findings in Propositus

Left Temporal Bone

The whole length of the endolymphatic duct is identified in step sections. The proximal endolymphatic duct near its origin in the vestibule from the union of the duct from the saccule with that from the utricle, shows marked overgrowth with many layers of ductular-lining epithelium, to such a degree that the cells almost fill the lumina of these structures. Just distal to this the vestibular aqueduct is slightly widened and the duct is filled by a lesion the appearances of which suggest an epithelial neoplasm composed of small regular glandular structures, which appear to be growing directly from the region of the normal epithelial lining of the endolymphatic duct. (Figs. 2a and b). The cells of the glandular structures are regular and frequently display clear cytoplasm. The ductular surface of the neoplasm at this level and even more extensively in the tumor tissue beyond (Figs. 3a, b and c) is covered by regular branching papillary processes lined by enlarged

cuboidal epithelial cells. A cyst lined by flattened epithelium is seen just below the tumor and in contact with it (Fig. 3b). Occasional mitotic figures are recognized in the epithelial cells of the neoplasm. The interior of the papillae shows vascular and connective tissue stroma. External to the papillae, in the endolymph space of the duct, are seen the outlines of large numbers of empty, poorly defined degenerate cells, probably desquamated from the proliferated epithelial cells of the papillae (Fig. 3b and c).

The tumor fills the duct in three consecutive step sections, thus indicating, from the known thickness of the sections (20 μm) and the distance between each step section (200 μm) a superior-inferior diameter for the tumor of about 420 μm (0.4 mm). The medial-lateral diameter of the tumor (i.e. along the length of the endolymphatic duct) measures approximately 1,000 μm (1.0 mm).

Immediately lateral (distal) to the tumor in the endolymphatic duct is a large epithelium-lined polypoid projection into the duct space. This is composed of hyaline pink-staining, birefringent material, interpreted as collagen [6] (Figs. 3a and b). Lateral (distal) to the large hyaline polypoid structure the endolymphatic duct shows a region of non-neoplastic but proliferative tubular appearance and irregular collagenous material within which are some variably-shaped, apparently calcified bodies, and concentrically laminated psammoma bodies (see below) The rest of the EDS is free from polypoid tissue or neoplasm, but there are irregular deposits of collagenous tissue on the inner surface of the duct. In the region of the medial lip the endolymphatic tube, now the endolymphatic sac, exhibits a small number of ductular outgrowths (see below).

The bony edge of the vestibular aqueduct near the neoplasm, but also in parts of the duct without neoplasm, displays an apparent erosion of the wall of the vestibular aqueduct (Fig. 3b) (see below). No definite invasion of the bony aqueduct wall by neoplasm can, however, be detected.

Fig. 2 (a) Low power view of proximal region of left endolymphatic duct showing mainly glandular part of endolymphatic tumor (arrow). Four basophilic papillae are seen at its lower (medial) pole. Below (medial) to the tumor the round pink area is a collagenous polyp. Upper arrowhead: utricle; Lower arrowhead: posterior semicircular canal. (b) High power view of glandular part of tumor showing many clear, vacuolated cells comprising the glands. The brown pigment in the lower left is probably melanin, which is commonly present in this tissue

Fig. 3 (a) Low power view of temporal bone section cut at 400 μ m inferior to that of Fig. 2a. The tumor in the endolymphatic duct is, at this level, composed entirely of papillary processes. Note the pink-stained polypoid structure just medial to the tumor and the duct lumen and epithelium just below that. Arrowhead: posterior semicircular canal. ((b) Higher power view of a) showing papillae of tumor and a

cyst lined by flattened pithelium. The bone of the vestibular aqueduct shows elongated spaces containing blood vessels. These are leaving or entering the lumen of the vestibular aqueduct. (c). Higher power view still of papillae of tumor showing fibrovascular cores and columnar epithelial covering. Note the outlines of empty degenerate cells external to the papillae

There is no evidence of hydrops involving the saccule, utricle or cochlear duct.

Right Temporal Bone

In sections of the right temporal bone the internal auditory meatus is conical-shaped, having been expanded by the a vestibular schwannoma, remains of which still distend that canal, where blood clot produced during the recent surgery is also seen (Fig. 4a). Higher power microscopic examination of the vestibular schwannoma shows regular spindle cells, partly in whorls (Verocay bodies), palisaded in places and areas of hyaline tissue, these features all being characteristic of schwannoma (Fig. 4b). The cochlear and vestibular spaces, both perilymphatic and endolymphatic, contain faintly eosinophilic exudate, a lesion usually found in large vestibular schwannomas (Fig. 4a). In the right EDS

there is no evidence of a papillary epithelial neoplasm. However, there is a brisk inflammatory exudate, composed of lymphocytes and macrophages, in the lumen within which many psammoma bodies (see below) are lodged. As in the left endolymphatic duct, hyaline polyps of collagenous tissue covered by normal endolymphatic duct epithelium are projecting into the lumen. Hyperplastic epithelial tubular outgrowths into connective tissue, (see below), are present in small amounts. In some areas of the right vestibular aqueduct an appearance of erosion is present in the bone adjacent to the endolymphatic duct epithelium.

Histological Features of the *Normal* Endolymphatic Duct and Sac

A study was made of the histological appearances of the *normal* EDS and the adjacent vestibular aqueduct

Fig. 4 (a) Right temporal bone showing conical-shaped internal auditory meatus which is filled with the remains of a vestibular schwannoma. Note eosinophilic exudate in all of the spaces of the

cochlea and vestibule. (b) Higher power view of vestibular schwannoma showing partly palisaded spindle cells and hyalinized areas in whorls (Verocay bodies) characteristic of vestibular schwannoma

structures in step sections of 66 temporal bones from subjects aged five to 82 years, to determine the feasibility of an origin of the tumor from the epithelial structures of the EDS and to assess the significance of the finding of psammoma bodies, polypoid collagenous structures and the apparent bony erosion that accompanied the tumor.

The *histological pattern of the EDS epithelium* is somewhat complex and varies with site. Examination of the full length of this blind-ended tube indicates two basic arrangements: (a) papillary ingrowths into the lumen and (b) complex tubular outgrowths away from the lumen into the connective tissue surrounding the duct/sac.

- a) In most of the EDSs, projections of epithelial-lined papillary ingrowths towards the duct lumen are seen in varying numbers. They may be simple or branching, the former more likely to occur in the proximal duct or distal sac, the latter in the osseous sac. Beneath the epithelial covering, capillary blood vessels can often be observed. Papillae may stretch across the lumen to reach the opposite side and may show acute-angled bends (Figs. 5 and 7).
- b) In the osseous part of the majority of mature endolymphatic sacs an additional pattern of complex tubular outgrowths from the main lumen into the surrounding connective tissue is identified. The main lumen is usually narrow in such areas and obliterated in places, appearing in cross section as a bilaminar closed structure. The lumina in the tubular outgrowths often appear similarly fused (Figs. 6a and b). In contrast, tubular outgrowths in some areas give rise to focal cystic dilatation, sometimes containing eosinophilic fluid and macrophages with ingested substance (Fig. 7). This arrangement of cellular tubular

Fig. 5 Normal proximal endolymphatic duct showing two bent papillae crossing the lumen (arrows). The macula of the nearby utricle is marked by an arrowhead

outgrowths is prominent in the osseous endolymphatic sac from about five years. Later in life it may extend distally for a short distance into the extraosseous sac.

Psammoma bodies are seen in the EDSs in 10 of the 66 mature endolymphatic duct/sacs examined, but are usually present singly (Fig. 8) not in groups, as was seen in both endolymphatic ducts/sacs in the present case. The psammoma bodies seem to arise from the epithelium of endolymphatic duct/sac. They are seen mainly in endolymphatic ducts and sacs of people above the age of 50 years.

Hyaline, collagenous, polypoid ingrowths are present in 26 out of 66 endolymphatic duct/sacs. They are usually not as large as the polyps seen in both endolymphatic ducts in the propositus and, like the psammoma bodies, are present only in the temporal bones of older subjects.

An appearance suggesting a possible *erosion of the inner surface of the vestibular aqueduct* was identified in 9 out of 66 cases of the mature temporal bones studied. Numerous vessels are present in the bone of the vestibular aqueduct and some enter the connective tissue surrounding the endolymphatic duct to form a network and leave to return to the bone. In some sections the bony canal surrounding a vessel entering or leaving endolymphatic duct may be identified, but the vessel itself may not be seen in those sections. Such appearance gives the erroneous impression of erosion of the endolymphatic duct/sac surface of the bone of the vestibular aqueduct [7].

Discussion

Site of and Spread from Origin

The tumor of the proximal endolymphatic duct described here is composed of a neoplastic accumulation of glandular and papillary epithelial tissue. Although measuring only up to about 1 mm in diameter, its histological appearances are those of the tumor described by Heffner [2] and now known as endolymphatic sac tumor. It is conceivable that this lesion may not be primary but a metastasis of an adenocarcinoma from another organ. No such primary malignant tumor, or other evidence of metastasis, was, however, found at autopsy of this patient.

Microscopic tumors confined to the endolymphatic duct or sac cannot yet be recognized by imaging using MRI or CT scans even if they are giving rise to cochlear-vestibular symptoms [4]. The sole method of detecting and study of such early tumors is by histological examination of the duct and sac at autopsy. Only a single such case has been previously reported [4]. This was a 40-year-old man with von

Fig. 6 (a) Normal endolymphatic sac of a 5 year-old male in the region of the medial lip (arrow). The endolymphatic sac emerges from the its intraosseous portion to the extraosseous position, where it is separated from the cranial cavity by meningeal membranes only.

Hippel Lindau disease, a terminal manifestation of which was bilateral tumors of the EDS. On the right side there was an extensive endolymphatic sac tumor invading the temporal bone to involve structures as far distant as mastoid air cells. On the left side illustrations define a papillary tumor confined to the lumen of the EDS, extending from the endolymphatic duct to the extraosseous sac on the dural surface. This case and the one described here confirm Heffner's concept of an origin of the neoplasm in the EDS.

In the paper by Lonser et al. [4] the neoplasm is purported to erode the contiguous region of the duct. The illustration shows, however, just a widening of duct or sac, a feature which is found in normal temporal bones; also a thin outer duct/sac epithelial lining, not penetrated by tumor, forms a layer between tumor and bone. It is thus

Fig. 7 Normal intraosseous sac in a 7-year-old male showing cellular papillary ingrowths and tubular cystic outgrowths. Note macrophages and eosinophilic fluid in lumen

The epithelium of the intraosseous sac is composed of complexly proliferated ducts. (b) Intraosseous endolymphatic sac epithelium from proliferated ductal outgrowths under higher power. Note marked vascularity of connective tissue surrounding sac

questionable in that case whether there really is erosion of bone and a similar possibility in the current propositus has been dismissed in the description given above in favor of normal passage of vessels through the interface of the vestibular aqueduct.

It seems more likely that early spread is from the ossified part of the duct/sac along the lumen of the vestibular aqueduct to the non-osseous part of the sac, as is shown in the autopsy temporal bone in the study by Lonser et al. [4]. There is no bony barrier here and the tumor can easily extend outside the temporal bone to produce a mass in the nearby cerebellopontine angle, which has been a frequent finding on imaging in published cases of this neoplasm.

The ductal and osseous sac origins of the tumor, surrounded as they are by bone, probably do invade bone at a late stage, and eventually tumor extensions will reach the

Fig. 8 Two psammoma bodies in normal much-narrowed intraosseous endolymphatic sac from a male of 76 years. Note tubular outgrowths containing eosinophilic fluid above

apical regions of the temporal bone and the middle ear from this source, as has also been well-described.

Tissue of Origin

This neoplasm is the only one with malignant potential to originate in the epithelia of the inner ear. Malignant neoplasms do not arise from nonmitotic tissues and all inner ear epithelia have been thought to be nonmitotic. What then is the tissue of origin of this neoplasm? In the study of normal epithelium of EDS reported here active hyperplastic areas with both papillary ingrowths and tubular outgrowths were revealed in most mature temporal bones. Such changes, called by Ng “a complex network of tubules” were shown by him to occur in endolymphatic sacs only after birth [8] and our unpublished investigations of the development of the EDS have confirmed that in fetal life the epithelium of those structures do not display such hyperplastic changes. The presence of papillary epithelial ingrowths and hyperplastic glandular outgrowths in the normal endolymphatic sac of the mature ear, suggests that origin of this tumor from such highly active epithelium is feasible.

Origin of the Molecular Basis of the Tumor

Von Hippel Lindau disease is an autosomal dominant syndrome resulting from a germ-line mutation in the *VHL* gene on chromosome 3. The normal *VHL* gene is a tumor suppressor gene [9, 10] and it seems likely that the diminution of tumor suppression activity which results from the mutation of that gene leads to the various manifestations of the disease: 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. Recent imaging studies have indicated that up to 16 percent of patients with Von Hippel Lindau disease have endolymphatic sac tumors [11]. The normal markedly proliferative epithelium of the EDS may be sensitive to a withdrawal of tumor suppressor function in cases with mutation of the *VHL* gene and thus liable to produce the endolymphatic sac tumor.

No manifestation of von Hippel Lindau disease, other than the endolymphatic duct tumor, was present at autopsy in this patient. Tissue from the patient was not available for investigation by molecular methods such as fluorescence in situ hybridization, for the presence of the gene mutation of von Hippel Lindau disease. Although rare, sporadic cases of endolymphatic duct tumor, i.e. those without von Hippel Lindau disease, are known to occur. The tumor

tissue in those cases may show, however, a *VHL* gene mutation similar to that in the germ line of patients with the disease [12].

Although a wide variety of neoplasms may be associated with von Hippel Lindau disease vestibular schwannoma has never been reported in that condition. Sporadic vestibular schwannomas are common in the general population—in one series having presented in one in 220 adult autopsies [13]. Neurofibromatosis 2 (NF2) is a less common genetic condition, which usually manifests itself in the earlier decades of life. It is characterized by multiple schwannomas, meningiomas and spinal neural tumors, but endolymphatic duct/sac tumors have not been described in association with NF2. No other explanation of the concomitance of vestibular schwannoma with endolymphatic duct tumor in the present case is realistic than that it is an association of a sporadic version of one with a sporadic version of the other.

Histopathology in the Investigation of the Origin of the Tumor in Cases at Surgery and Autopsy

In an analysis of clinically uninvolved “tumor-free” EDS tissues of von Hippel Lindau patients in both autopsy and surgical specimens, Gläsker et al. claim to have discovered a series of microscopic abnormalities with morphologic similarities to those of endolymphatic sac tumors which they characterized as “multifocal sites of *VHL*-deficient cell proliferations from which tumorigenesis may or may not occur”. These were papillary ingrowths, cysts and “vacuolated clear cells similar in appearance to renal cell carcinoma” [14]. Papillary ingrowths, including polypoid collagenous ingrowths and cysts are common, however, in normal endolymphatic ducts and sacs, as shown above. “Vacuolated clear cells” is an imprecise description which is not made more specific in the photographs provided by the authors. It therefore seems doubtful whether the findings of Gläsker et al. do in fact indicate potentially neoplastic transformation of cells induced by mutation of the *VHL* gene; they could, according to the description given in my study of normal EDS features above, be simply aspects of the normal histology which resemble those of neoplasia. Pathologists should be wary of such appearances when interpreting histopathological findings in surgical biopsy or autopsy material taken from the EDS with regard to possible malignant or premalignant changes.

Psammoma bodies are typically found in papillary epithelial neoplasms in other parts of the body, being frequent in papillary adenocarcinoma of the thyroid gland and papillary serous adenocarcinoma of the ovary. They have not been described in endolymphatic sac tumor. I observed, however, multiple psammoma bodies in the present case in

the endolymphatic duct near, but not actually within the small papillary tumor on the left side. Many psammoma bodies were, moreover, also found in the *right*, endolymphatic duct in the present case, although there was no overt EDS tumor in that situation. The significance of the multiplicity of psammoma bodies in the EDSs of the propositus is unknown. It is shown here also that they may be found in small numbers in the normal EDS where they appear to take their origin.

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