Head and Neck: Ear: Endolymphatic Sac Tumor (ELST)

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Identity

Alias
Low Grade Papillary Adenocarcinoma of the Endolymphatic Sac, Papillary Adenoma of the Endolymphatic Sac.

Note
Endolymphatic sac tumors (ELSTs) are rare tumors of the petrous temporal bone. Classified as mastoid papillary tumors of unknown origin, these tumors were synthesized into a new, distinct clinicopathological entity by Heffner in 1989. Initially described as a low grade papillary adenocarcinoma, their histologic appearance and apparent lack of metastatic potential has since persuaded most practitioners to reclassify them as papillary adenomas. ELSTs can arise sporadically or in association with von Hippel-Lindau (VHL) disease.

Classification

Note
The differential diagnosis for ELSTs includes all intrinsic temporal bone neoplasms (most commonly paraganglioma) as well as metastatic papillary thyroid carcinoma, metastatic renal cell carcinoma, and choroid plexus papilloma, the latter three of which are similar in appearance to ELSTs histologically.

Clinics and pathology

Disease
Endolymphatic sac tumors are rare. As a recognized, distinct entity, ELSTs are relatively new. The first reported case of a tumor arising from the endolymphatic sac was discovered during decompression of the endolymphatic sac for presumed unilateral Ménière’s Disease in 1984. Although benign, ELSTs can be locally destructive. They present with hearing loss, tinnitus, facial nerve weakness or paralysis, vertigo, and can be lethal. CT imaging demonstrates erosion of the posterior petrous temporal bone with occasional intratumoral calcification. MRI tumor signal is isointense to brain and demonstrates gadolinium enhancement and heterogeneous signal intensity from intratumoral calcification and vascularity.

Etiology
The synthesis of sporadic temporal bone papillary tumors into a distinct clinicopathological entity was proposed in 1989 by Heffner, with the anatomic origin of these tumors being the endolymphatic sac. Knowledge of this tumor has grown, expedited in part by its association with VHL disease, yet many aspects are still poorly understood.
MRI T1 weighted axial images of the brain at the level of the endolymphatic sac and internal auditory canal. The top view without gadolinium contrast shows moderate expansion of the endolymphatic sac and duct on the right. The bottom view with gadolinium contrast shows contrast enhancement of the endolymphatic sac on the right.

CT axial image of the temporal bones at the level of the endolymphatic sac and internal auditory canals. The vestibular aqueduct on the right is markedly widened directly behind the internal auditory canal and vestibule, in contrast to the appearance of the vestibular aqueduct on the left, which is thin and nondescript. The bony erosion and widening of the vestibular aqueduct on the right is highly suggestive of a neoplastic or otherwise destructive process within the endolymphatic sac, consistent with an ELST.
Initially described as a low grade papillary adenocarcinoma, the histologic appearance and apparent lack of metastatic potential of these tumors has convinced some to reclassify them as benign papillary adenomatous tumors. The high overall survival following surgical resection, despite locally aggressive behavior, is likely due to the underlying benign histology of the tumor.

**Epidemiology**

Over 175 case reports of ELSTs have now been reported in the literature. The majority of these are single case reports of a practice group or university. As the majority of these case reports do not disclose the population size of their patient base, it is difficult to assess the true incidence of these tumors. ELSTs tend to afflict women more than men with an overall female to male ratio of 2:1 in a review of the literature.

**Clinics**

The most common presenting complaints were aural, with hearing loss occurring in nearly every reported patient, followed by tinnitus, aural fullness, and imbalance. The symptoms of pulsatile tinnitus, otalgia, otorrhea, vertigo, and facial paresis were also present in some patients. Cranial neuropathies were also diagnosed either at the time of presentation or following treatment. The most commonly involved nerve was the facial nerve, with preoperative facial paresis or paralysis in 43% of patients. In patients with larger tumors or in those who delayed presentation for decades after onset of initial symptoms, multiple cranial neuropathies were present including trigeminal, glossopharyngeal, and vagal nerves.

From a statistical standpoint, a vascular tumor eroding the temporal bone and cranial base is likely to be a paraganglioma, and likely a glomus jugulare tumor. Large glomus tumors as well as large ELSTs can both present as pink or purple masses encroaching on the middle ear and external auditory canal. Glomus tumors exhibit a characteristic "salt and pepper" tumor appearance on MRI, but this heterogeneity in signal reflects the vascularity of such tumors and is not pathognomonic. The heterogeneity in signal seen in large ELSTs - arising from hypervascularity as well as intra-tumoral hemorrhage and/or calcification - can often mimic glomus tumors in this respect. This is not necessarily problematic, as management would proceed similarly for either histologic type of tumor: preoperative embolization followed by total tumor resection via the appropriate lateral skull base approach.

**Pathology**

ELSTs are highly vascular and are comprised of papillary cystic structures lined with a simple cuboidal or columnar epithelium. Siderophages and cholesterol clefts are seen, as are clear, vacuolated cells. Nuclear pleomorphism is not pronounced, and mitoses are rare. Immunohistochemistry and special staining may aid in differentiation of papillary tumors of question-able origin. ELSTs usually stain positive for cytokeratin, vimentin, and epithelial membrane antigen, as well as stain on Periodic acid-Schiff (diastase sensitive). Some papers have also reported sensitivity to glial fibrillary acid protein; however, most authors have had poor tumor reactivity to glial fibrillary acid protein. Papillary thyroid metastasis to the temporal bone may be differentiated by positive reaction to thyroglobulin immunohistochemistry. Transthyretin has been shown to exhibit differential expression in choroid plexus papillomas with little to no expression in ELSTs.
Histological appearance of ELST. HE stain, low power magnification, demonstrating the characteristic papillary cystic architecture of these tumors.

**Treatment**

Surgical resection is the primary modality of treatment for ELSTs. Despite the benign histologic nature of these tumors, complete resection appears crucial for ensuring success. Total tumor resection is clearly the treatment of choice, as only one patient with reported complete resection had subsequent recurrence. Although the most common presenting symptom was sensorineural hearing loss, many patients, particularly those with VHL disease, present with small ELSTs and consequently present with serviceable hearing. VHL patients are unique in that all undergo active surveillance and cranial imaging for hemangioblastoma as part of their VHL disease management. Subsequently, ELSTs in these patients are frequently diagnosed early, with relatively little delay between onset of audio-vestibular symptoms and identification of tumor. This significantly affected surgical decision making, as 32% of patients underwent hearing conservation procedures while 68% underwent hearing ablative procedures. In patients with excellent preoperative hearing and a small ELST, such a hearing conservation approach may be warranted. However, the completeness of tumor resection should not be compromised for the sake of hearing conservation. Half of patients undergoing hearing conservation approaches with subtotal resection followed by adjuvant radiation therapy had regrowth of tumor.

In some tumors, total resection cannot be achieved without risk of catastrophic loss of function or death, and in these patients subtotal resection may be warranted. Patients who have subtotal resection may benefit from postoperative radiotherapy, but there still remains a roughly 50% risk of tumor regrowth and therefore close surveillance is warranted as re-resection may be necessary. Stereotactic radiotherapy has shown no increased benefit above standard fractionated radiotherapy in survival or recurrence rates, and
subtotal resection followed by stereotactic radiotherapy has uniformly resulted in tumor regrowth. There are no reported cases of radiation therapy and/or stereotactic radiotherapy used as the primary modality of treatment for ELSTs.

**Evolution**

There are currently no reported cases of spontaneous metastatic dissemination of ELSTs in the literature. Recently however, two reports have surfaced describing metastatic disease following subtotal resection. The first was a reported case of ELST drop metastasis with dissemination onto the ipsilateral cerebellar convexity beyond the original tumor site in a patient who had undergone previous subtotal resection and radiotherapy. A second case of drop metastasis of ELST involved the spine, manifesting after multiple subtotal resections and three courses of stereotactic radiosurgery.

These seminal reports serve to illustrate the importance of complete tumor removal on initial resection in order to minimize both recurrence and metastatic seeding. The oncologic principle of complete tumor extirpation of ELSTs, despite their benign histology and absence of spontaneous metastasis.

**Prognosis**

Overall survival characteristics for all reported cases of ELSTs are: 74% no evidence of disease, 20% alive with disease, and 4% died of disease, for the reporting periods.

ELSTs are histologically benign yet sometimes destructive, highly aggressive lesions. They show excellent response to primary surgical resection, with or without adjuvant radiotherapy. Complete tumor removal on initial resection is crucial. Hearing preservation should not take precedence over complete tumor removal, as adjuvant radiotherapy does not ensure against tumor recurrence, which can be devastating and lethal. In addition, drop metastases following subtotal tumor resection have now been reported. In patients with VHL disease, regularly scheduled audiometry and surveillance MRI are vital to early detection of ELSTs, which can optimize the opportunity for hearing preservation without compromising tumor control.

**Genetics**

The current literature suggests that approximately one third of all ELSTs are associated with VHL disease. VHL disease is an autosomal dominant familial cancer syndrome. VHL disease affects approximately 1 in 39,000 people. It encompasses a variety of neoplasia both benign and malignant including renal cell carcinomas, central nervous system hemangioblastomas, retinal hemangioblastomas, pheochromocytomas, and cysts of the kidneys, pancreas, and epididymis. The gene responsible for VHL disease is a tumor suppressor and it has been mapped to chromosome 3p25. The VHL gene product pVHL forms a multi-protein complex that contains elongin B, elongin C, Cul-2, and Rbx1.

The pVHL complex has a role in oxygen sensing. The VHL gene regulates vascular endothelial growth factor VEGF, and inactivation of the gene promotes VEGF overexpression and angiogenesis. In addition, its loss of function mutation can increase expression of hypoxia-inducible factor HIF1, stimulating angiogenesis and tumorigenesis. In VHL disease, it is believed that tumors arise when both an inherited germline mutation and a loss-of-function mutation of the wild-type VHL gene are present.

In addition, it has been shown that somatic mutations to the VHL gene locus at 3p25/26 are detected even in cases of sporadic ELSTs, that is, in non-VHL patients. Genetic sequencing analysis of the 3p25 VHL gene locus in both sporadic and VHL-associated ELSTs demonstrates nucleotide substitution as well as deletion/frameshift errors.

Even though temporal bone lesions were described in patients by Lindau in 1926, the association of these tumors with VHL disease was not made until recently. This clinical association has been confirmed at the molecular level with mutations in the VHL gene identified in endolymphatic sac tumors in VHL patients. Approximately 10% of patients with VHL disease have ELSTs, and approximately 30% of VHL patients with ELSTs have bilateral tumors. This variable phenotypic expression may be a reflection of VHL gene function secondary to the type of mutation present.

Indeed, VHL disease has been found to have phenotypic expression consistent within members of a family, thus implying a singular, conserved mutation within affected families. VHL disease is categorized into two familial types, with type 1 being without pheochromocytomas and type 2 being with pheochromocytomas. There is further subclassification of type 2 into type 2a, low risk for developing renal cell carcinoma, and type 2b, high risk for developing renal cell carcinoma. Clinical presentation type correlates with genetic mutation type: type 1 families usually have deletion or truncation mutations, whereas type 2 families usually have missense mutations.

If a family history of VHL disease exists, or if the diagnosis of VHL disease is made in the absence of an ELST, then early routine audiologic screening can allow for early tumor detection and the possibility of hearing preservation surgery should ELST develop. Positive identification of tumor on MRI with gadolinium is necessary prior to surgery: to date,
surgical exploration in VHL patients with audiovestibular symptoms but without MRI abnormalities has not been documented and is not recommended.

**Genes involved and proteins**

**VHL**

**Location** 3p25.3

**DNA / RNA**

The VHL gene is a tumor suppressor gene mapped to chromosome 3p25/26.

**Protein**


**References**


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*This article should be referenced as such:* Diaz RC. Head and Neck: Ear: Endolymphatic Sac Tumor (ELST). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(3):321-326.