

Original Article

Endolymphatic sac tumor: clinical, radiological and pathological analyses of four cases

Tingting Liu¹, Lei Chen²

Departments of ¹Pediatric Hematolog/Oncolog, ²Pathology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

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Abstract: Endolymphatic sac tumor (ELST) is a neuroectodermal tumor of the temporal bone and has high prevalence in von Hippel-Lindau (VHL) disease. ELST presents diagnostic challenge due to its rarity and the variety of other tumors potentially showing similar features. We reviewed 4 patients of ELST and the clinical, radiologic and histopathological findings were described. Three cases were sporadic and 1 case was associated with VHL disease. Clinically, the most common symptoms were tinnitus, vertigo and hearing loss. Computed tomography or magnetic resonance imaging revealed posterior temporal bone lesions in these 4 cases. Morphologically, tumor cells were observed as papillary, glandular or cystic architecture. Immunohistochemistry analysis demonstrated the positive reactivity with CK, CK7, and negativity of TG and TTF-1. Tumor cells showed low proliferation index of Ki-67 from few than 1% to 2%. Clinical presentation, radiographic and morphological description and immunophenotypic features play a paramount role in achieving an accurate diagnosis of ELST.

Keywords: Endolymphatic sac tumor, endolymphatic sac, von Hippel-Lindau disease

Introduction

Endolymphatic sac is derived from neuroectoderm and is located adjacent to the posteromedial surface of the temporal bone. It is a component of the membranous labyrinth providing inner ear homeostasis for endolymph resorption [1]. Endolymphatic sac tumor (ELST) is a rare hypervascular tumor in the posterior petrous bone, which was firstly described by Hassard in 1984 [2]. In 1989, Heffner characterized ELST as an identical tumor entity, referring to it as a “low-grade adenocarcinoma” [3]. ELST has been published under various terminology in the literature such as Heffner tumor, aggressive papillary middle ear tumor, or low-grade adenocarcinoma of endolymphatic sac origin. These tumors arise sporadically or coexisting with von Hippel-Lindau (VHL) disease [4].

ELST is originated from the epithelium of the endolymphatic sac. With tumors growing, ELST may destruct the retrolabyrinthine petrous bone and extent into the supra- as well as infralabyrinthine and mastoidotympanic regi-

ons, resulting in varying degrees of tinnitus, vertigo and hearing loss [5]. Imaging findings usually reveal the erosion of temporal bone including the endolymphatic sac, retrolabyrinthine, and presigmoid region. Similar to other tumors with characteristics of hypervascular, ELST may be misdiagnosed as paraganglioma, glomus tumor, and other temporal tumors radiographically [6]. Morphologically, ELST presents epithelial features, such as papillary architecture, glandular formation and a colloid-like structure, which also overlaps with other papillary lesions, including metastatic thyroid carcinoma, middle ear adenoma, and chorioid plexus papilloma [7].

We presented here 4 patients of ELSTs, and the clinical symptoms, radiographic features and histopathological traits were described.

Materials and methods

Study patients

This study was based on a review of 366 cases with available surgical samples in the meatus

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Table 1. Clinical features in 4 cases with endolymphatic sac tumor (ELST)

Case No.	Age (y)	Gender	Symptoms				Diagnosis	Surgery	Follow-up (m)
			Tinnitus	Hearing loss	Vertigo	Others			
1	34	Male	Yes	Yes	Yes	No	ELST	Yes	9
2	70	Male	Yes	Yes	Yes	Otalgia and ear bleeding	ELST	Yes	20
3	59	Female	Yes	Yes	No	Ear liquid flow	ELST	Yes	16
4	37	Female	Yes	Yes	No	Walking lability and facial paralysis	ELST with VHL disease	Yes	22

VHL, von Hippel-Lindau.

Table 2. Imaging features in 4 cases with endolymphatic sac tumor (ELST)

Case No.*	Tumor side	Tumor size (mm)	Bone erosion	Locations			
				Temporal bone	Cerebellopontine angle	Occipital bone	Other sites
1	Left	19	Yes	Yes	Yes	No	No
2	Right	20	Yes	Yes	Yes	No	Vestibule, semicircular canal and external acoustic meatus
3	Left	40	Yes	Yes	No	Yes	Jugular foramen and external acoustic meatus
4	Right	42	Yes	Yes	Yes	Yes	No

*Case numbers are identical with the patient number used in Table 1.

auditorius (middle, inner, and ear) and cerebellopontine angle, from September 2012 to November 2015. Four patients in different regions of China were identified as ELSTs and enrolled. Computed tomography (CT) scan and magnetic resonance imaging (MRI) were evaluated among patients. Diagnosis was confirmed by histological and immunohistochemical analyses. Formalin-fixed paraffin-embedded tissues were available of the 4 cases. Clinical information was recorded for each patient including age, gender, date of initial diagnosis, symptoms and signs at presentation, treatment and follow-up data.

Histology and immunohistochemistry

Formalin-fixed, paraffin-embedded tumor biopsies were stained with hematoxylin and eosin (HE) at initial diagnosis. Immunohistochemical assay was performed using a panel of monoclonal and polyclonal antibodies, as follows: Cytokeratin (CK) (clone AE1/AE3, DAKO, Glostrup, Denmark, 1:100); CK7 (clone K72.7, DAKO, 1:100); CK19 (K19.2, DAKO, 1:400); CK20 (clone KS20.4, DAKO, 1:100); Glial fibrillary acidic protein (GFAP) (clone GA5, DAKO, 1:800); Neuron-specific enolase (NSE) (clone E27, DAKO, 1:400); Epithelial membrane antigen (EMA) (clone GP1.4, QuanHui, Shanghai, China, 1:600); Ki-67 (clone MIB-1, DAKO, 1:100); Thyroglobulin (TG) (clone 2H11+6E1, DAKO, 1:200); Thyroid transcription factor (TTF)-1 (clone SPT24, QuanHui, 1:400); Carcinoembry-

onic antigen (CEA) (clone COL-1, DAKO, 1:400); S100 (clone 4C4.9, DAKO, 1:1000); CD34 (clone QBEnd/10, DAKO, 1:400). The immunohistochemical stain was considered positive when greater than 25% of the tumor cells reacted positively.

Results

Clinical features

Clinical characteristics of 4 cases with ELSTs were summarized in **Table 1**.

Of the 4 cases, 2 cases were female and 2 cases were male, with a median age of 59 years (range, 34-70 years). Three cases were sporadic ELSTs, and the other case had a known history of VHL disease with hemangioblastomas, renal cell carcinoma and pancreatic adenomas.

Among the 3 cases of sporadic ELSTs, the most common symptoms were unilateral tinnitus, vertigo and aggressive hearing loss, followed by otalgia (1/3), ear bleeding (1/3), and ear liquid flow (1/3). The case with VHL disease presented with bilateral tinnitus and aggressive hearing loss, and neurologic symptoms including imbalance and facial nerve dysfunction.

Followed by surgery, the follow-up durations ranged from 9-22 months, with a median follow-up time of 20 months.

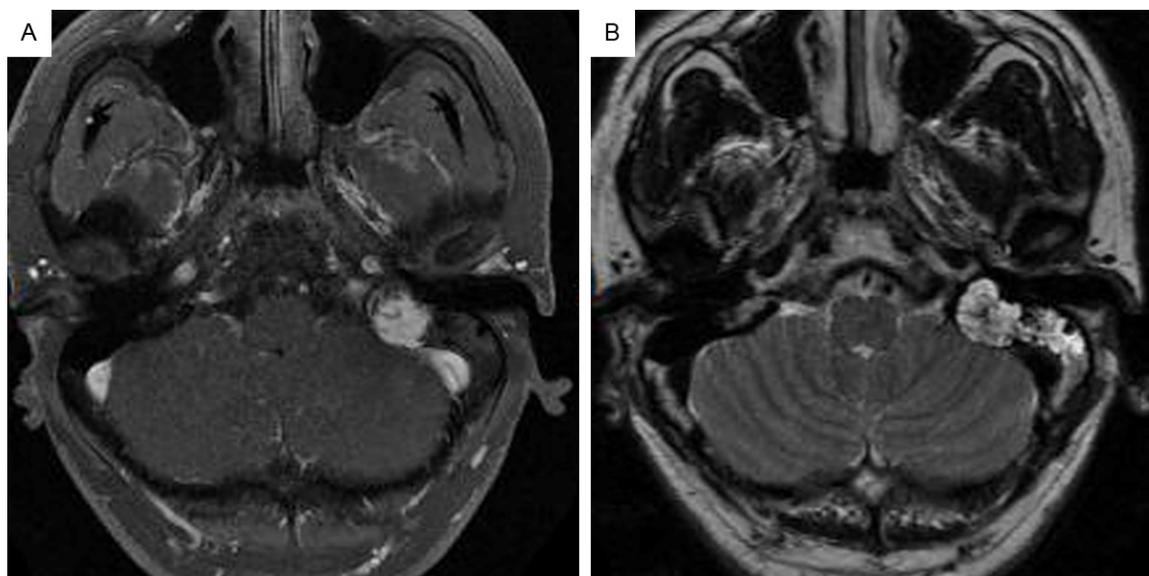


Figure 1. Radiologic characterization of endolymphatic sac tumor (ELST). A: Magnetic resonance images scan revealed a 19 mm×18 mm mass in the left petrous segment of temporal bone which was irregular, heterogeneous signal intensity on T1-weighted axial images. B: The periphery of the lesion appeared hyperintensity on the T2-weighted axial images.

Radiological manifestations of ELST

Imaging features of 4 cases with ELSTs were shown in **Table 2**. The 4 cases of ELSTs were identified unilaterally, including 2 cases on the right side, and the other 2 cases on the left. Tumors ranged from 19 to 42 mm in diameter.

CT or MRI scan of the 4 cases showed the extensive destruction of petrous bone, in which 3 cases with extension of cerebellopontine angle, 2 cases of occipital bone, 2 cases of external acoustic meatus, 1 case of vestibule and semicircular and 1 case of jugular foramen.

On MRI, tumors involved a mastoid process of the petrous bone which was irregular, cystic and heterogeneous (**Figure 1**). Hypointense and heterogeneous signal intensity on T1- and T2-weighted axial images were shown in 3 cases with sporadic ELSTs. Hypointense bone spicules and flow void on T1- and T2-weighted images presented heterogeneous enhancement after injection. Irregular markedly hypointense areas on both the T1- and T2-weighted images within the lesions represented the necrosis, calcification, or residual bone after destructive invasion. The patient with VHL showed hyperintensity on both T1- and T2-weighted images, suggestive of intratumor hemorrhage.

Pathological findings

The specimens were received as aggregate of gray-red fragments and were noted to be soft to moderate in consistency with partly cystic appearance.

Microscopically, tumors were considered as papillary-cystic glandular architecture. On high magnification, the papillary proliferation was lined by a single layer of low, cuboidal to columnar epithelial cells with uniform nuclei, eosinophilic cytoplasm and indistinct cell borders. There were minimal cellular pleomorphism and rare mitotic activity and necrosis was observed. The stroma of the papillary fronds was richly vascularized and generally composed of thin fibrovascular tissue, focal fibrotic areas with hemorrhage, cholesterol clefts, hemosiderin deposits, mononuclear cell infiltration and inflammatory cells (**Figure 2A, 2B**).

As shown in **Table 3**, ELST tumor cells showed positive staining with CK (4/4), CK7 (3/3) (**Figure 2C**), CK19 (2/2), and variable reactivity with EMA (2/3) and GFAP (3/4). CK20 (**Figure 2D**), TG, TTF-1 (**Figure 2E**), CEA and S-100 immunoreactivity were negative expression. The Ki-67 immunostaining showed very low proliferation index from few than 1% to 2% (**Figure 2F**).

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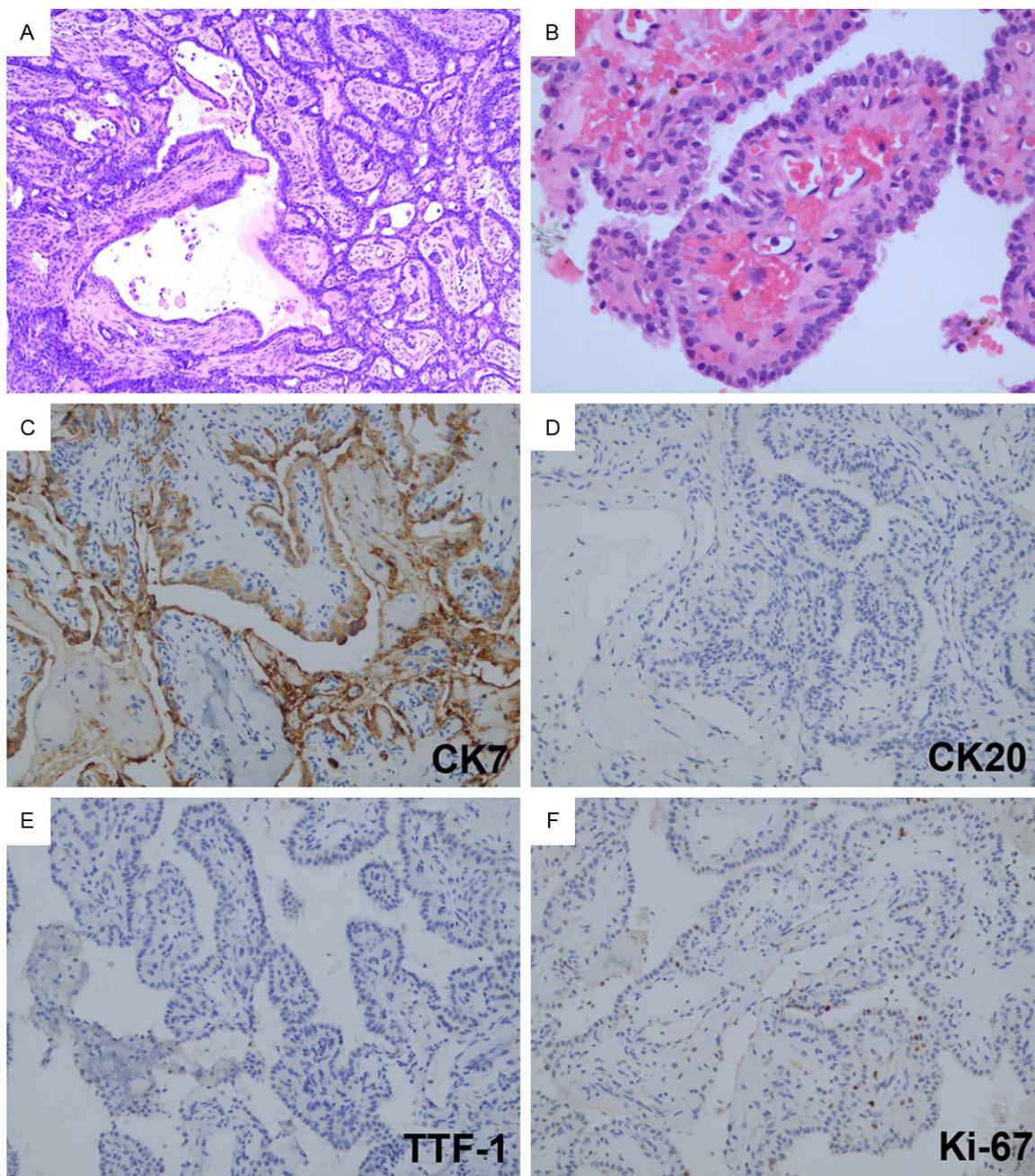


Figure 2. Histopathologic characterization of ELST. A: Histopathologic examination of the tumor showed papillary and cystic structures (Hematoxylin and eosin, HE, original magnification ×100). B: The papillary structure was lined by cuboidal epithelial cells (HE, original magnification ×400). C-F: Immunophenotype of ELST. C: Cytoplasmic immunostaining for CK7 showed positive expression (original magnification ×400). D: Negative immunohistochemical reaction for CK20 (original magnification ×400). E: The tumor cells exhibited negative expression of thyroid transcription factor (TTF)-1 (original magnification ×400). F: Immunostaining for Ki-67 showed a proliferation index of 1% (original magnification ×400).

Discussion

ELST was described as slow-growing but locally aggressive tumors causing bone erosion and invasion to adjacent structures [8]. Tissue ori-

gin of ELST was controversial and the epithelium of a middle-ear origin was presumed in the past [9]. In 1995, Megerian et al considered that ELST originated in the endolymphatic duct or sac, based on the microscopic and FISH

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Table 3. Immunohistochemical features in 4 cases with endolymphatic sac tumor (ELST)

Case No.*	CK	CK7	CK19	EMA	GFAP	CK20	Ki-67	TG	TTF-1	CEA	S100
1	+	+	+	+	+	-	<1%+	ND	-	-	-
2	+	+	+	+	+	-	1%+	-	-	-	-
3	+	+	ND	-	-	-	2%+	-	-	-	-
4	+	ND	ND	ND	+	ND	ND	ND	ND	ND	ND

*Case numbers are identical with the patient number used in **Table 1**. ND, not detected.

analyses [10]. Moreover, due to extreme rarity of ELST, it would be challenging to diagnose or treat with the disease precisely.

The clinical features of ELST were dependent on tumor size and growth directions. The most common symptoms were tinnitus, hearing loss and vertigo, as reported in our results and previous study [5]. The above symptoms, however, were not specific for ELST, and may also be misdiagnosed or confused with other diseases, such as Meniere disease [11]. Early imaging analyses were needed if no proper disease was identifiable for these symptoms.

In this study, CT and MRI imaging showed that our 4 cases of ELSTs were located in endolymphatic sac invading the temporal bone and 3 cases extending to cerebellopontine angle. Due to the similarities of tumor sites and hypervascularity, ELST may be indistinguishable from other lesions, including paraganglioma or glomus jugular tumor. Our 3 sporadic ELST patients were initially misdiagnosed as paraganglioma or glomus jugular tumor from imaging perspective. Small ELST may be primarily centered in the retrolabyrinthine portion of the petrous bone, between the internal auditory canal and the sigmoid sinus, in the area of the vestibular aqueduct. In contrast, paraganglioma or glomus jugular tumor arose predominantly from infralabyrinthine site [12]. The primary location of small lesion was helpful for the differential diagnosis, but large mass of ELST would be easily misdiagnosed with paraganglioma and middle ear papillary tumor radiographically.

Morphologically, tumor cells of ELST showed a papillary structure containing cuboidal or columnar cells with fibrous stroma and numerous microvessels and destructed temporal bone, which was distinguishable from paragangliom. Moreover, our results showed that tumor

cells were positive for CK and CK7, which were helpful for excluding the diagnosis of paraganglioma immunohistochemically. The histopathological differential diagnosis of ELST also included metastases thyroid carcinoma. In our cases, tumor cells of ELST were negative for TG and TTF1, which helped distinguish ELST from metastases thyroid carcinoma. Thus, the final diagnosis may be reached through histopathological and immunohistochemical evaluation of the tumor specimens.

ELST occurred more frequently in patients with VHL disease, accounting for 16% of patients with ELST having VHL disease [4]. VHL disease was a hereditary multi-tumor syndrome, which was known as hypervascular tumors, such as hemaniblastomas, renal cell carcinomas, and pheochromocytomas [13, 14]. VHL disease was more likely to be female. In our study, the VHL case had evidence on imaging of ELST and presented bilateral tinnitus and aggressive hearing loss, and neurologic symptoms, which were consistent with previous reports [15].

In this study, we reported 3 cases of sporadic ELST and 1 case of ELST associated with VHL disease, and the detailed clinical, radiographic as well as histopathologic features were described. The proper diagnosis of ELST was difficult. Precise preoperative anatomic localization based on radiographic interpretation, morphological features and immunophenotype are important to achieve an accurate final diagnosis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lei Chen, Department of Pathology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China. Tel: 86-21-25077219; E-mail: chenlei021@sina.com

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