

CASE REPORT

Giant intracranial endolymphatic sac tumor (ELST). Case presentation and histogenetic considerations

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Abstract

We present a giant tumor of the skull base compressing the brain in a 40-years-old man. The tumor was polycystic at imaging. Its histopathology, immunohistochemical profile and long evolution suggest an endolymphatic sac tumor (ELST), a rare case of neoplasia. Since the patient had multiple otolaryngological procedures in his medical history, a possible traumatic pathogenesis could be suspected. On the other way, some immunohistochemical aspects found in our case may imply a histogenesis divergent from that currently accepted. This could be from either the organ of Corti or some local cells that generate a resemblance with a systemic tumor, the so-called benign mesothelioma. Further studies are needed in order to clarify this topic.

Keywords: giant endolymphatic sac tumor (ELST), calretinin, histogenesis, organ of Corti, benign mesothelioma.

Introduction

Skull base tumors represent a challenge for pathologists, otorhinolaryngologists, and neurosurgeons. In such cases, complications following surgical procedures are hard to avoid, especially in malignant tumors [1]. Most of adult cases are invasive meningiomas, but other tumors can also be found in this region, such as local extensions from neighboring structures – airways and orbit carcinomas, and rarely middle ear tumors. Among the latter, the most frequent are rhabdomyosarcomas, paragangliomas, and carcinomas [2]. Lipomas, angioleiomyomas, cavernous hemangiomas are also present, but are rare in this location [3–6]. The internal ear is also mentioned as a source of tumors with intracranial extension and among these, endolymphatic sac tumor (ELST) appears to be the most frequent [7].

ELSTs are aggressive papillary lesions located within the temporal bone and most likely derived from the endolymphatic sac [7]. They have variable malignancy, sometimes infiltrating the bone and extending intracranial.

The case we present is special because of its radiological, clinical and immunohistochemical aspects.

Clinical report

In his medical history, the patient – a 40-years-old man – underwent repeated, almost annually, surgical

procedures in several neurosurgery clinics for a polycystic tumor progressively extending from the skull base into the posterior fossa.

In 1987, he was diagnosed with an acute right otitis media, treated by myringotomy. Subsequently, in the first postoperative year, the patient suffered iterative local interventions for chronic infection with purulent discharge, including a petromastoid exenteration and drainage, when he also presented purulent meningitis with coma.

In 1989, a cerebellopontine mass was revealed, but the patient refused the surgery. One year later, the tumor was removed by a suboccipital retromastoid craniotomy. Afterward, seven surgical procedures have been done at 2–3 years intervals.

At each intervention, variable amounts of tumor tissue were excised. At current admission, the patient presented with headache, vertigo, ataxia and several clinical findings on the right side: neocerebellar syndrome, facial nerve paralysis, deafness and hypoesthesia in the trigeminal territory. Magnetic resonance imaging revealed a very large, polycystic and septate tumor, which have destroyed the temporal bone, reaching the right cerebellopontine angle and compressing the brain stem. The tumor was also massively extending upward, with marked indentation of the occipital lobe and diencephalon (Figures 1 and 2).

The surgical approach was also retromastoid, with only partial resection of the tumor caused by vigorous intraoperative bleeding.

The patient was discharged in an improved condition with no further recommendations. At last follow-up, one and a half year the last surgery and 20 years after the onset of the disease, the patient is still in good condition.

Pathologic report

At macroscopic examination, the surgical sample consisted of small fragments of brown, firm tissue with no recognizable organ elements. The samples were fixed in 10% neutral formalin and routinely processed for histology. Hematoxylin & Eosin and Masson's trichrome were performed on the fixed material.

The histological examination showed a tumor with both papillary and polycystic pattern. The papillae have been covered by cuboidal or columnar cells disposed around a richly vascularized fibro-connective central core (Figure 3).

Other tumor areas consisted of cystic spaces limited by large amounts of collagen and lined by flat epithelial cells (Figure 4). Rare foreign-body giant cells and cholesterol clefts were scattered within the collagen structures (Figure 5).

The slides from previous surgery procedures were also retrieved from the archives and they disclosed histological aspects similar to those found at the current examination. Immunohistochemistry was performed on the paraffin-embedded material using the EnVision+ Dual Link System Peroxidase kit (Dako, Carpinteria, CA, USA), according to the manufacturer's instructions. Primary antibodies against the following antigens were used: vimentin (1:50), CD31 (1:40), S100 (1:500), GFAP (1:50), EMA (1:75), NSE (1:50), Ki67 (1:50) (Dako, Glostrup, Denmark); KL1-cytokeratin (1:200), CD34 (1:250) (Immunotech, Marseille, France); VEGF (1:100) (Santacruz Biotechnology, Santacruz, CA, USA); SMA (1:4000) (Sigma, Saint Louis, MO, USA); calretinin (1:50) (Novocastra, Newcastle Upon Tyne, UK). Primary antibodies against the following antigens were used: vimentin (1:50), CD31 (1:40), S100 protein (1:500), GFAP (glial fibrillary acidic protein) (1:50), EMA (epithelial membrane antigen) (1:75), NSE (neuron-specific enolase) (1:50), Ki67 (1:50) (DakoCytomation, Glostrup, Denmark); KL1-cytokeratin (1:200), CD34 (1:250) (Immunotech, Marseille, France); VEGF (vascular endothelial growth factor) (1:100) (Santacruz Biotechnology, Santacruz, CA, USA); SMA (smooth muscle actin) (1:4000) (Sigma, Saint Louis, MO, USA); calretinin (1:50) (Novocastra, Newcastle Upon Tyne, UK).

The epithelium lining the cysts was diffusely positive for KL1 (Figure 6), EMA (Figure 7), calretinin (Figure 8) and vimentin (Figure 9), and focally for NSE and VEGF (Figure 10). SMA, CD31 and CD34 were positive only in the stromal vessels, and negative in the papillary epithelium. GFAP and S100 protein were negative in the tumoral cells, as well as Ki67.

Discussions

The endolymphatic sac tumor (ELST) is a relatively recent discovery [8]. Its main characteristics are slow clinical progression and long evolution, papillary or microcystic histology and severe bleeding at surgical intervention [9]. Our case exhibits all these mentioned features.

ELST can be associated in 7% of cases with von Hippel-Lindau (VHL) syndrome, an autosomal dominant disease caused by a deletion or mutation of a tumor suppressor gene on the short arm of 3p chromosome (3p25–26) [10, 11].

Clinically, VHL is characterized by the association of various neoplasms including central nervous system and retinal hemangioblastomas, renal cell carcinomas, pheochromocytomas, ELSTs, pancreatic endocrine tumors and multiple cystic tumors involving pancreas, kidney, adrenal, epididymis and ovary [12–14]. In our case, all these neoplastic changes, in particular the cerebellar hemangioblastoma (the hallmark of VHL syndrome) as well as the family history of VHL syndrome (except ELST) were absent. Therefore, we could rule out the possibility of VHL. Some clinicopathological associations have critical importance in our case.

The histopathological aspect of ELST is special, currently allowing a differential diagnosis from other tumors commonly found in this location, such as neurinoma, meningioma or glomus jugulare tumors. On the other hand, the differential diagnosis with cerebellopontine angle tumors with papillary structure has to be made, mostly if partial resections are performed: papillary meningioma and ependymoma, choroid plexus papilloma and metastatic papillary adenocarcinoma [15]. However, immunohistochemistry is mandatory for making a definite differential diagnosis with most of the aforementioned tumors (Table 1).

Papillary meningioma is CD31, VIM, and sometimes S100, and CK7 positive, but GFAP negative; ELST is negative for CD31. Papillary ependimomas are GFAP positive, and choroid plexus papilloma is sometimes GFAP positive, unlike ELSTs that are always GFAP negative [16]. Our case showed co-expression of KL1, vimentin, EMA and NSE in the epithelium of the cysts. Similar immunohistochemical features were previously reported [17–19].

SMA, CD31, CD34, and VEGF were performed to quantify the intratumoral microvascular density (angiogenesis) a factor that correlates with a difficult resection caused by abundantly intraoperative bleeding. Unlike literature data, which describe an intense and diffuse reaction [17], the presence of only zonal positivity for VEGF in the papillary epithelium in our case (Figure 10) needs to be studied in the future. The tumor occurred after a series of inflammatory-infectious and traumatic local events (several surgical interventions for otomastoiditis) not previously reported as associated with cases of ELST.

Table 1 – Immunohistochemical differential diagnosis of papillary tumors of the cerebellopontine angle

Antibody	ELST	Meningioma	Ependymoma	Choroids plexus papilloma	Metastatic papillary adenocarcinoma
CK	+	S	S	+	+
VIM	+	+	+	+	S
S100	S	R	S	+	S
EMA	+	S	S	+	+
GFAP	-	-	+	S	-
NSE	+	R	S	+	S
SYN	-	-	-	+	-
SMA	-	-	-	-	-
CD31	-	+	-	-	-
CD34	-	-	-	-	-
VEGF	S	-	-	-	S

S – sometimes positive; R – rare cells may be positive; CK – cytokeratins; VIM – vimentin; EMA – epithelial membrane antigen; GFAP – glial fibrillary acidic protein; NSE – neuron-specific enolase; SYN – synaptophysin; SMA – smooth muscle actin; VEGF –vascular endothelial growth factor.

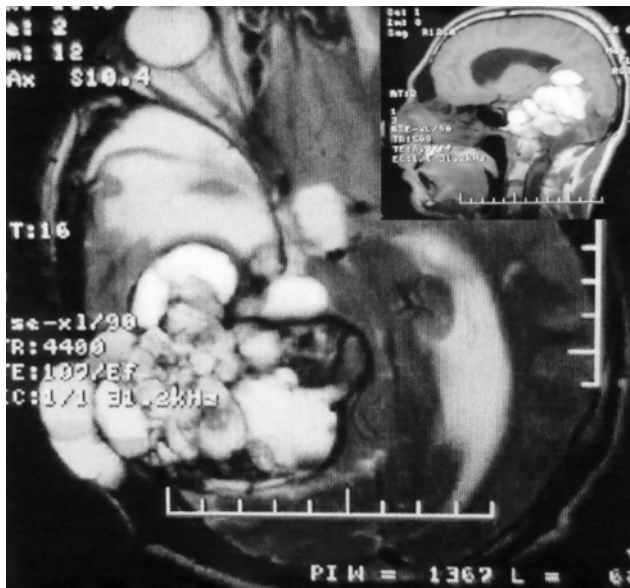


Figure 1 – T2-weighted MRI scan with contrast administration reveals a very large, polycystic and septate tumor, which destroyed the temporal bone and reached the cerebellopontine angle (insert – sagittal view)



Figure 2 – Coronal T1-weighted MRI contrast enhancing view of the tumor compressing the adjacent brain structures

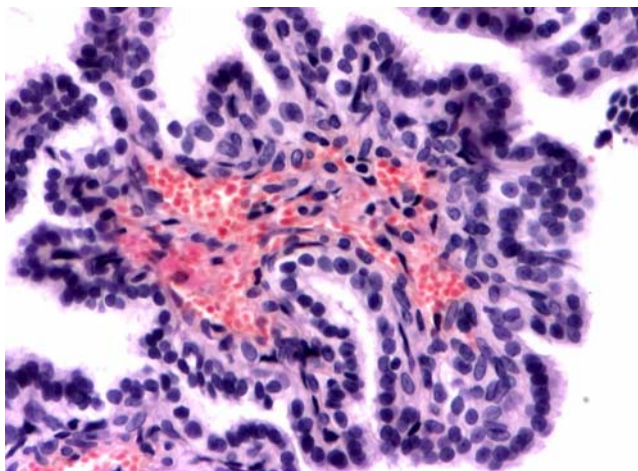


Figure 3 – The tumor shows a papillary structure, with cuboidal or columnar cells disposed around richly vascularized fibroconnective central cores (HE stain, x20)

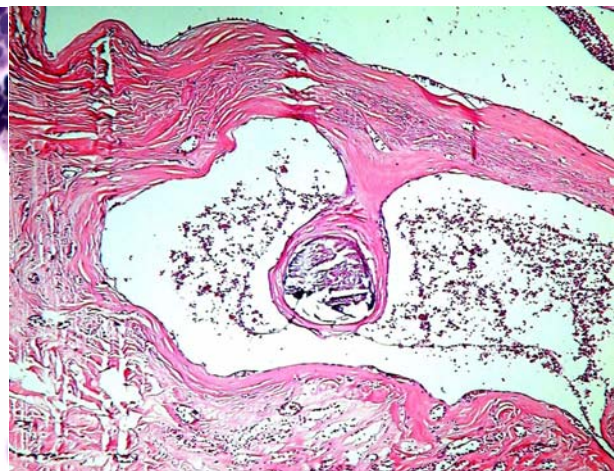


Figure 4 – Other tumor area disclosing cystic spaces lined by epithelial cells (HE stain, x10)

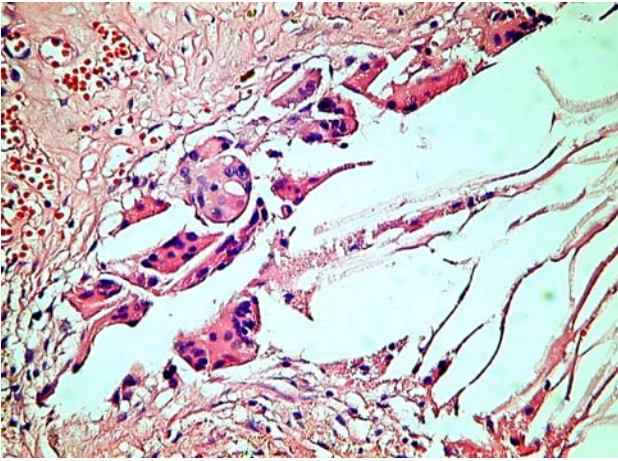


Figure 5 – Foreign-body giant cells scattered within the collagen structures (HE stain, $\times 40$)

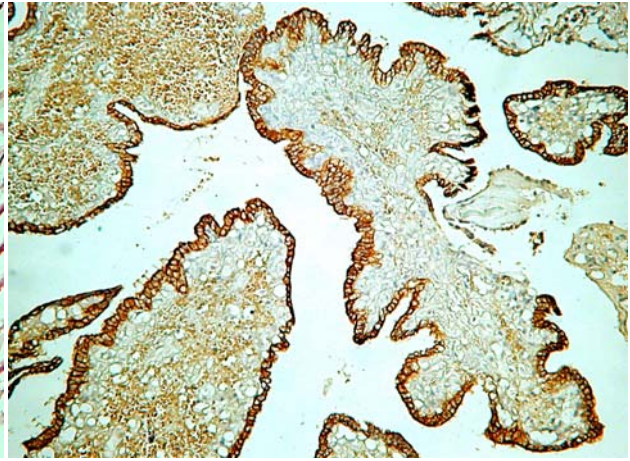


Figure 6 – KL1 cytokeratin is strongly expressed in the epithelium covering papillae (IHC, $\times 20$)

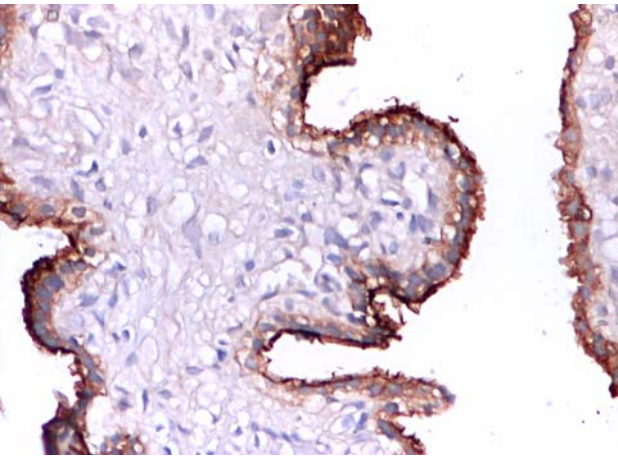


Figure 7 – Positive reaction for EMA in the papillary epithelium (IHC stain, $\times 20$)

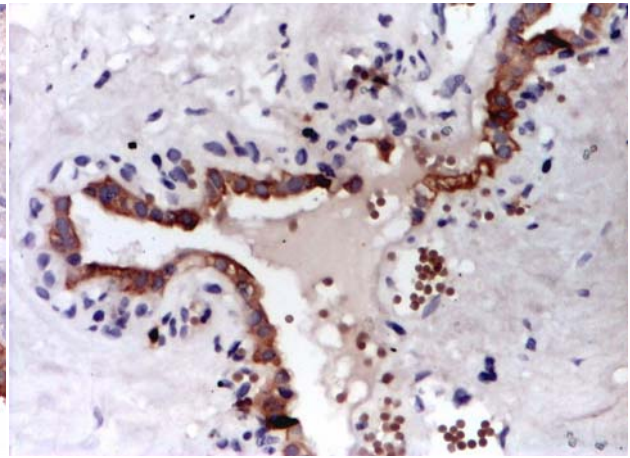


Figure 8 – Positive reaction for calretinin in the tumoral cells (IHC stain, $\times 20$)

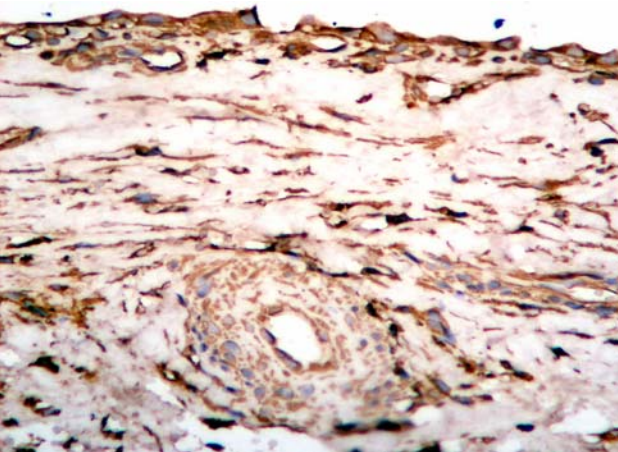


Figure 9 – Epithelial cells showing strong positive reaction for vimentin (IHC stain, $\times 40$)

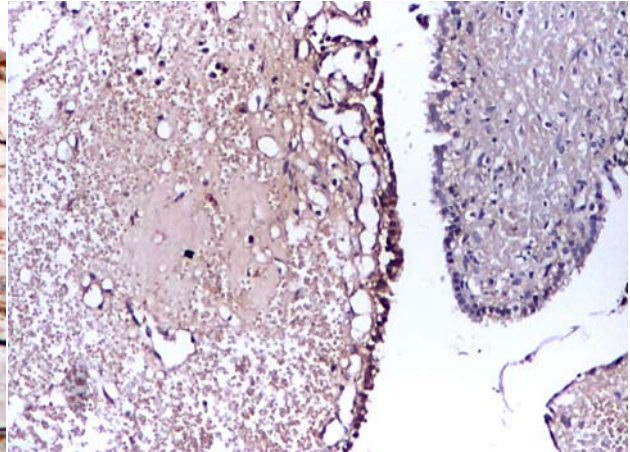


Figure 10 – Focal positive expression of VEGF in the epithelium of the left hemorrhagic papilla, while the right one remains negative (IHC, $\times 10$)

On the other way, such inflammatory-infectious and traumatic factors are frequently associated with an abdominal tumor, the benign mesothelioma, a peculiar entity that shares with our case many clinicopathological features: a polycystic mass

apparently formed by retention cysts, usually following local aggressions and chronic inflammations [20]. Since benign mesotheliomas express calretinin, we performed this IHC stain as a possible confirmation of traumatic pathogenesis.

The tumor was positive, a reaction for the first time reported in ELST.

The immunophenotype we found in this case, with co-expression of calretinin, cytokeratin and vimentin was described in the literature only in benign and malignant mesotheliomas with various locations (not previously reported at cephalic level) [21–24]. This immunopositivity shared by mesotheliomas and the tumor found in our patient sustains a possible inflammatory-infectious and traumatic etiology (also not described to date in ELST, to the best of our knowledge). The histological picture also very resembles between the two entities.

On the other hand, same antigenic associations founded in this case show also some overlap with the immunohistochemical aspects of several normal structures from the organ of Corti. Cytokeratins appear positive in the epithelial cells on the whole surface of the organ of Corti and vimentin is detected in inner and outer pillar cells [25]. Cytokeratin and vimentin co-expression is detected in supporting (Deiters' and pillar), Claudius' and external sulcus cells [26]. Calretinin can be positive in inner hair cells, Deiters' cells and Hensens' cells [27–29]. These complex immunohistochemical aspects partly or totally match with the immunophenotype of our case. As a result, a possible histogenesis from modified Deiters' cells of the organ of Corti is very likely, at least in our patient.

Other authors have also raised the question of a different origin of ELST [30] and the topic needs further investigation.

Regarding the prognosis, the benign histology (absence of atypia, pleomorphic nuclei and mitoses) correlated with negative Ki67 labeling index and with the very long evolution suggest a favorable outcome despite the giant dimensions of the tumor.

☐ Conclusions

We present an infrequent giant skull base tumor with intracranial extension and controversial histogenesis. Its potential origin from modified cells of the organ of Corti or other local cells of the internal ear is possible. Local inflammatory-infectious and/or traumatic events could be a potential oncogenic trigger. The particularly large extension, long evolution, difficult surgical approach and potential diagnostic difficulties make this tumor a challenging entity.

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