What a Neurosurgeon Should Know About the Endolymphatic Sac: Part 2 – Diagnosis and Management of the Endolymphatic Sac Tumors

O Que um Neurocirurgião Deve Saber Sobre o Saco Endolinfático: Parte 2 – Diagnóstico e Manejo dos Tumores do Saco Endolinfático

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Abstract

Objective This article is divided into three parts. In the second part of this review, the authors focus on describing the endolymphatic sac tumor and presenting illustrative cases.

Methods A review of previous studies, from 1957 to 2021, from basic and translational research using human and animal endolymphatic sac (ES) tissue or cells, as well as other reviews on this theme.

Results The ES is an inner ear structure, which is responsible for the homeostatic regulation, as well as endolymphatic fluid volume control, immune response etc. One of the possible alterations of the ES is the ELST, a low-grade malign neoplasm that originates from the epithelium of the endolymphatic duct and sac. The clinical presentation of the ELST includes hearing loss, tinnitus, headache, and vertigo. The

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diagnosis in the early stages is rare, given that this group of symptoms is very similar to other, more common, diseases such as the Meniere syndrome. Its diagnosis is made by computed tomography (CT), magnetic resonance imaging (MRI), immunohistochemistry, and confirmed by histopathology. However, none of these examinations are part of the pathological guidelines for ELST. The treatment for ELST in the early stages has a high rate of success.

Conclusion The ELST is a very difficult diagnosis due to its presentation. Furthermore, the interactions between ELST and the Von Hippel-Lindau disease usually result in a more aggressive condition. Despite the difficulty of the diagnosis, doing it early increases the chances of successful treatment.

Resumo

Objetivo Este artigo é dividido em três partes. Na segunda parte desta revisão, os autores focam em descrever os tumores do saco endolinfático (TSE) e apresentar casos ilustrativos.

Métodos Revisão de estudos prévios, de 1957 até 2021, de pesquisa básica até translacional usando tecidos ou células do saco endolinfático (SE) humanas e animais, além de revisões sobre o assunto.

Resultados O SE é uma estrutura situada na orelha interna, e é responsável pela regulação homeostática, controle do fluido endolinfático, resposta imune, etc. Uma das possíveis alterações do SE são os TSE, uma neoplasia de crescimento lento, com agressão local e de baixo grau, que se origina do epitélio do saco e do ducto endolinfático. A apresentação clínica do TSE se dá com perda auditiva, zumbido, cefaleia e vertigem. O diagnostico em estágios iniciais é raro devido a apresentação clínica similar a diversas outras patologias mais comuns como a Síndrome de Ménière. O diagnóstico é feito com por tomografia computadorizada (TC), ressonância magnética (RM), imuno-histoquímica e confirmada com histopatologia. Entretanto nenhum desses exames está nas diretrizes das patologias que mimetizam o TSE. O tratamento para o TSE em estágios iniciais tem uma alta taxa de sucesso.

Conclusão O TSE é uma patologia de difícil diagnostico devido a sua apresentação. Além disso, a interação entre o TSE e a doença de Von Hippel-Lindau resulta em uma condição mais agressiva da doença de maneira geral. Apesar dessa dificuldade de diagnostico, fazê-lo em estágios iniciais aumenta muito as chances de sucesso no tratamento.

Palavras-chave
- saco endolinfático
- tumores
- clínica
- diagnóstico
- tratamento
- neurocirurgia

Introduction

In the first part of this article, we studied the endolymphatic sac's (ES) microanatomy and physiology. Evidence supports the idea that the ES has a very distinctive function when compared with the structures around it, such as homeostasis regulation of the inner ear, endolymphatic fluid volume control, immune response, elimination of inner ear cellular debris and floating otoconia, membranous labyrinth pressure management, acid/basic transport, and secretion of substances.[1–11]

The ES, despite being only 3 mm in diameter, does not have a very variable location inside the inner ear.[8,12] Almost every alteration in this structure can cause a massive problem to hearing, including hearing loss.[13] One of these possible problems is the endolymphatic sac tumor (ELST), a slow-growing, locally aggressive, low-grade malign neoplasm that originates from the epithelium of the endolymphatic duct and sac.[14]

In this review, our aim is to elucidate the clinical presentation, diagnosis, and treatment of the ELST.

Methodology

This article is divided into three parts. In this second part, we review the ELSTs and present illustrative cases. We focused on evidence collected from 1957 to 2021, including basic and translational researches using human and animal ES tissue or cells, as well as previous reviews about the subject, using the terms individually and combined: *Endolymphatic sac tumor*, *Clinic*, *Diagnosis*, *Treatment*, *Neurosurgery*. Literature inclusion criteria were articles in written English, including individual case studies and long-term follow-up studies; the exclusion criteria were duplicate studies with high

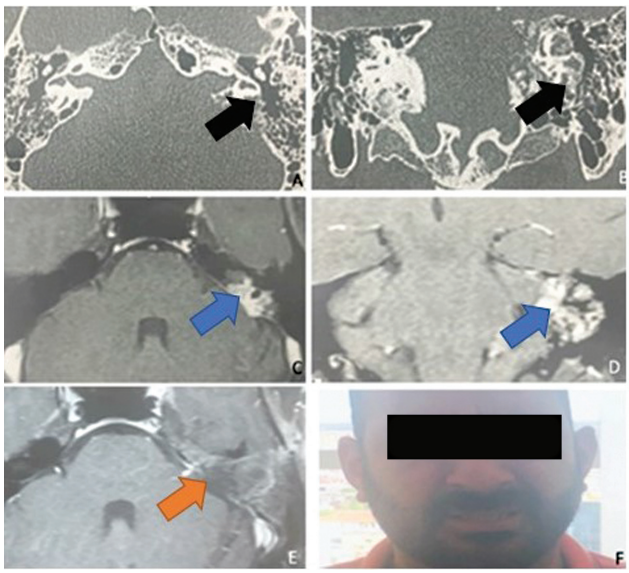

Fig. 1 Case 1, axial (A) and coronal (B) CT scan of the temporal bone in the bone window, showing destruction on the petrous portion of the temporal bone. Axial (C) and coronal (D) MRI scans of the T1 with gadolinium showing tumor inside the mastoid portion of the temporal bone, with involvement of the Trautmann triangle's dura mater. MRI of the T1 with gadolinium 3 months after surgery, showing total resection of the lesion (E) with facial nerve preservation (F). Black arrow: expansive lesion with erosion of the temporal bone's petrous portion. Blue arrow: tumor seen in the MRI scan. Orange arrow: late postoperation exam showing complete tumor resection.

similarity and articles that not fit into the including criteria. First, we briefly reviewed the basic aspects of the ELST, followed by a more detailed explanation of its clinical presentation, diagnosis, and treatment. This study may provide a basis for planning early-stage diagnostic guidelines.

Results

Illustrative Cases

Case 1

A patient with conduction hyperacusis in the left ear for 6 months came to our clinic with a cranial CT showing left temporal lobe bone erosion, and an MRI with gadolinium suggesting ESLT. A transmastoid approach was used to make a full resection of the tumor (►**Fig. 1**). Histopathology confirmed the ELST, and the patient do not have a tumoral recurrence during 6 years of attendance (►**Fig. 2**).

Case 2

A 37-year-old woman with right ear vertigo and deafness for 4 years. In the last few months, she'd noticed otorrhagia in the same ear. Developed facial paralysis (HB 3) and right symmetry in the last month (►**Fig. 3**,**4**,**5**,**6**).

Basic Aspects of the ELST

The ELST is an aggressive, slow-growing, with low-grade malignancy that originates from the epithelium of the endolymphatic duct and sac.[14] In 1957, the term *ceruminoma* was first coined to the adenomas and adenocarcinomas of the external auditory canal. However, the origin of middle and inner ear adenomas is still unclear and, consequently, the origin of ELST is still in debate. Some authors support that it originates from aberrant ceruminous glands, while others postulate that the tumors arise from native middle ear mucosa.[14,15]

It is known that 11% of the patients with the Von Hippel-Lindau (VHL) disease will develop ELST.[16,17] Thus, the epithelium of the ES can produce an aggressive papillary lesion (APL); ELST may also present a follicular pattern (AFL) on light microscopy.[14]

The APL refers to a papillary protuberance with arranged cuboidal or low columnar cells. On the other hand, the AFL is represented by cists full of thyroid follicles proteinaceous debris, although thyroglobulin stains were not found. Some ELST may have both alterations.[18]

According to the literature, ELST is cytokeratin and vimentin-positive, and the majority will be S-100 positive. Furthermore, ELST is chromogranin negative, which can differentiate them from the paraganglioma, and transthyretin negative, which distinguishes them from the choroid plexus tumor. Also, they are thyroglobulin negative, unlike metastatic thyroid cancer.[19,20]

Clinical Presentation

The most common symptom observed by Poletti[21] in his study was unilateral deafness. This hearing loss can be explained by the association with the Meniere disease.[22] Additionally, the most common symptoms include tinnitus and vertigo.[19]

The ELST originates at the temporal bone's posteromedial aspect, and from there it can spread posteriorly to the cerebellopontine angle.[14,19] This expansion can cause brainstem compression and, consequently, several neurological deficits.[14,19,20] Another possible tumor spread is the lateral way which can affect the facial nerve or mimic middle ear infection symptoms.[14,19] The jugular foramen syndrome (glossopharyngeal neuralgia, hypoglossal paralysis, and motor disturbances) or cerebellopontine angle syndrome (hearing loss, facial paralysis, and balance disturbance) are both also possible impairments.[19] Death only happened in cases of vascular issues and high intracranial pressure.[14]

One of the biggest challenges in the ELST is the distinction from the Meniere disease.[22] The clinic presentation of this pathology is tinnitus, unilateral hearing loss, aural fullness, and vertigo,[9] which mimics the symptoms of the ELST, since it create a barrier for the endolymph reabsorption as it grows, producing excess fluid and secondary hydrops (SNHL).[14]

Another important association for ELST is the Von Hippel-Lindau (VHL) disease, which is an autosomal-dominant, multisystem disorder characterized by cerebellar hemangioblastomas, retinal angiomas, renal or pancreatic cysts, renal cell carcinoma, pheochromocytomas, and other visceral tumors, according to Wick et al.[14] Despite having no clinical mimetics, 11% of the patients with VHL will develop ELST, and 30% of those will have severe impairment with bilateral lesions.[14,16,17] The average age in which ELST patients

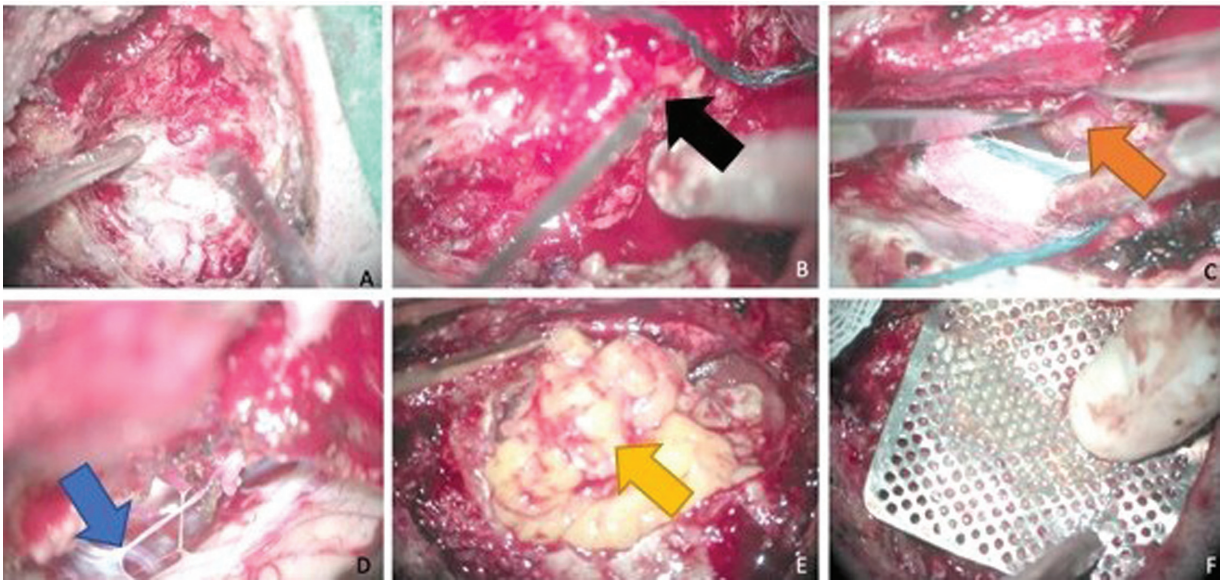

Fig. 2 Case 1, intraoperative vision. The mastoidectomy is performed (A). The mastoid portion of the facial nerve is identified through anatomic parameters and facial nerve stimulation, in cases where the nerve is not in the bone canal (B). The Trautmann triangle is incised, and the tumor is identified (C). Removal of the tumor along with the Trautmann triangle dura mater (D). The mastoid cavity is sealed with abdominal fat (D). Before that, the Eustachian tube is sealed with muscle. The titanium mesh position in a steady way, making pressure over the fat is crucial to avoid cerebrospinal fluid (CSF) leak. Thereunto, it is important to do a bone flat fixation with screws into the temporal bone edges (F). Black arrow: mastoid segment of the facial nerve being localized with 0.05 mA electrical stimulus. Orange arrow: tumor is adherent to the dura of the Trautmann triangle. Blue arrow: anterior inferior cerebellar artery (AICA). Yellow arrow: abdominal fat is used to avoid CSF leak.

without VHL express symptoms was 52.5 years, whereas in the group with VHL, the average was 31.3 years.[23,24] Thus, ELST in patients with VHL can occur in younger people and more aggressively.

Diagnosis

Two of the most important exams to neurosurgery, computed tomography (CT) and magnetic resonance imaging (MRI) scans, also make themselves indispensable for the diagnosis of ELST.[14] Contrast CT presents with enhancement of soft-tissue masses with bone erosion over the ES. In late presentations, intratumor and kidney-shaped calcifications are seen.[14,25,26]

Examinations through MRI also show the heterogeneous focus of low and high signal intensity on T1 and T2 imaging. The hyperintense areas on T1 represents intraparenchymal hemorrhage and the hypointense reflect residual bone or prominent calcification. With contrast the image often shows heterogeneous patterns.[14,25,26]

Regardless of the CT and MRI scans, the differential diagnosis is still challenging. Paraganglioma (glomus jugular or glomus tympanicum), choroid plexus tumor, metastasis, eosinophilic granuloma, meningioma, arachnoid granulation, aneurysmal bone cyst, or a primary bone tumor are some the pathologies that can be seen with similar patterns to the ELST.[14,26,27] However, the immunohistochemical technique is one the few that can differentiate the previously described entities.[14]

The diagnosis can be confirmed by histopathologic analysis.[22] It reveals bone and tissue infiltrations, surrounded by neoplastic lesions and fibrous core. The histopathologic difference of low and high magnification is the clear cells presentation in the higher one.[22]

In 2004, Bambakidis et al.[28] made a classification for ELST based on tumor extension. Furthermore, they suggested surgical options for each of the grades (►**Table 1**).

The patients' clinical history related to VHL must be investigated. In the absence of this data, according to Magerian et al., it is mandatory to obtain a detailed history of first-degree relatives for problems such as retinal angiomas, renal or pancreatic cysts, pheochromocytomas, or other manifestations of VHL. In the cases of suspected VHL, the patient's family must be called for genetic tests and consulting.[23]

Despite the difficult diagnosis, doing it in the early stages is crucial for better chances of total resection surgery and hearing preservation; specially in VHL patients who have an increased risk for bilateral ESLT and, consequently, total hearing loss.[28]

Treatment

The technique for removal of both sides of the dural sleeves around the ES that shows the most effective results has been called retrolabyrinthine-transdural approach (RTA) or the retrolabyrinthine posterior necrosectomy approach.

For the RTA procedure, the patient is placed supine and positioned with the head turned away from the surgeon. The patient's hair is shaved, but usually head pins aren't necessary. A facial nerve monitor is used to identify possible injuries in this structure during the procedure.

With all the preincision steps done, a mastoidectomy is performed to identify the horizontal semicircular canal and the facial nerve. Afterwards, the following structures are

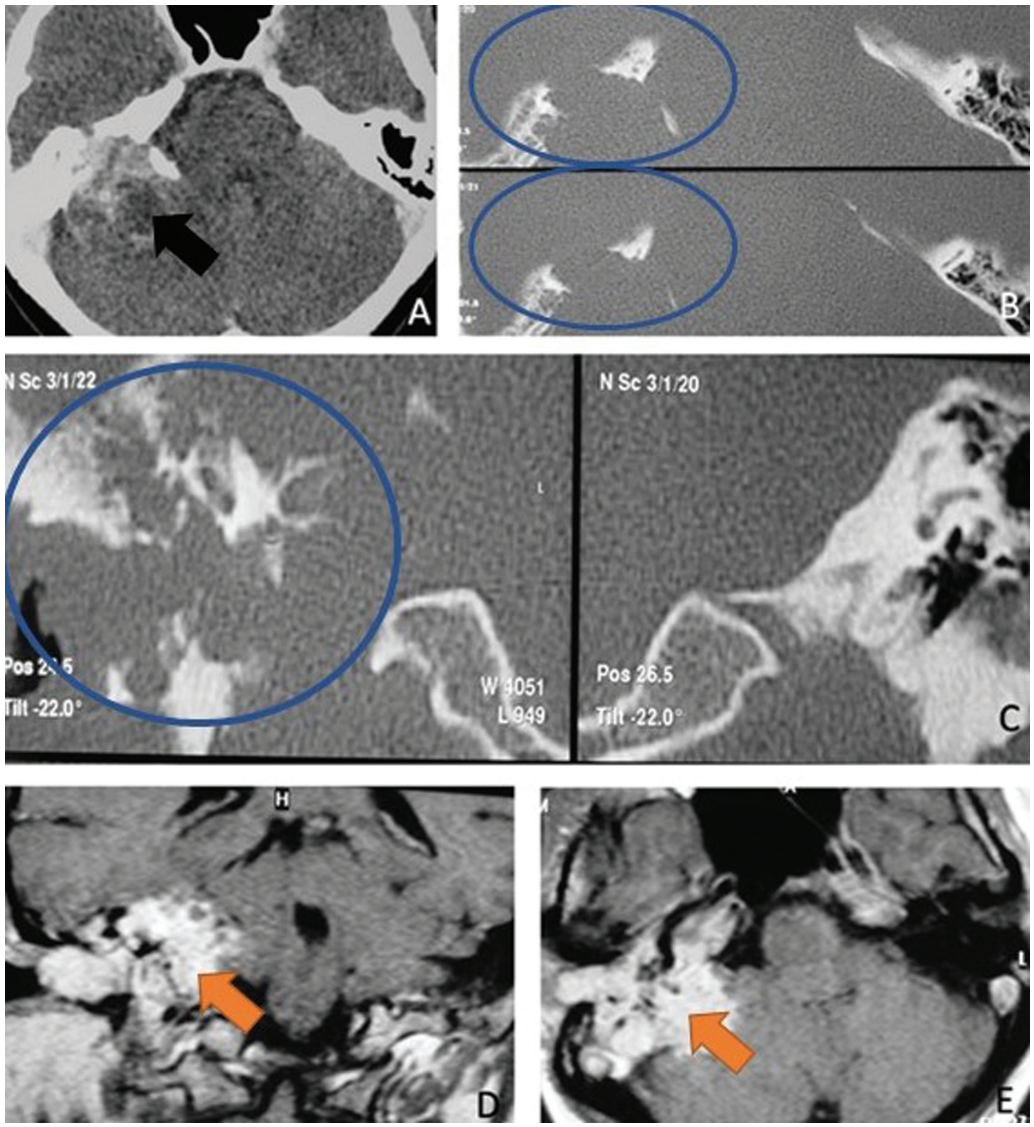

Fig. 3 Case 2, CT scan revealed a right angle cerebellopontine tumor, with erosion of the mastoid part of the temporal bone (A). The axial (B) and coronal (C) CT scans in the bone window, showing erosion and destruction of the temporal bone. Coronal (D) and axial MRI scans of the T1 with gadolinium (E) show that the tumor is occupying the mastoid part of the temporal bone with an extension on the cerebellopontine angle and external auditory canal. Black arrow: cerebellopontine angle tumor. Blue circles: bone lesion in the temporal bone petrous portion. Orange arrow: expansive lesion seen in MRI.

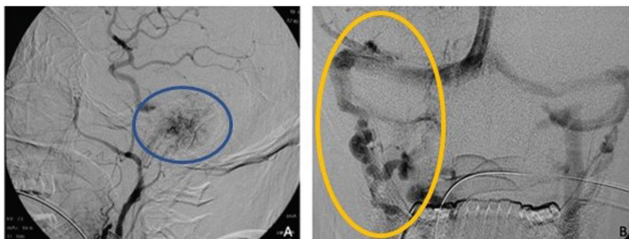

Fig. 4 Case 2, Angiography showing tumoral nutrition by the external carotid artery branches that were embolized during this procedure (A). The right side of the Sigmoid sinus was obstructed by the tumor on the preoperatory period (B). Blue circle: expansive lesion after embolization. Yellow circle: venous flow alteration through expansive lesion.

skeletonized: the tegmental dura, the sinodural angle, and the jugular bulb. Normally, after those steps, the ES and the tumor can be seen.[23]

When the ELST is identified, the endolymphatic duct is followed with a diamond burr and the tumor is resected. If the posterior semicircular canal is injured, it can be sealed quickly with bone wax; however, lesions in this structure need to be avoided as much as possible, to decrease post-op complications.[23]

After the tumor removal, the bone around the tumor must be extracted with a margin of 0.5 cm, as the sac and duct are removed en bloc. The antrum is then sealed with bone wax and the dura with abdominal fat.[23]

In two studies,[29,30] with a total of 9 patients affected by grade I tumors, the RTA uniformly resulted in hearing

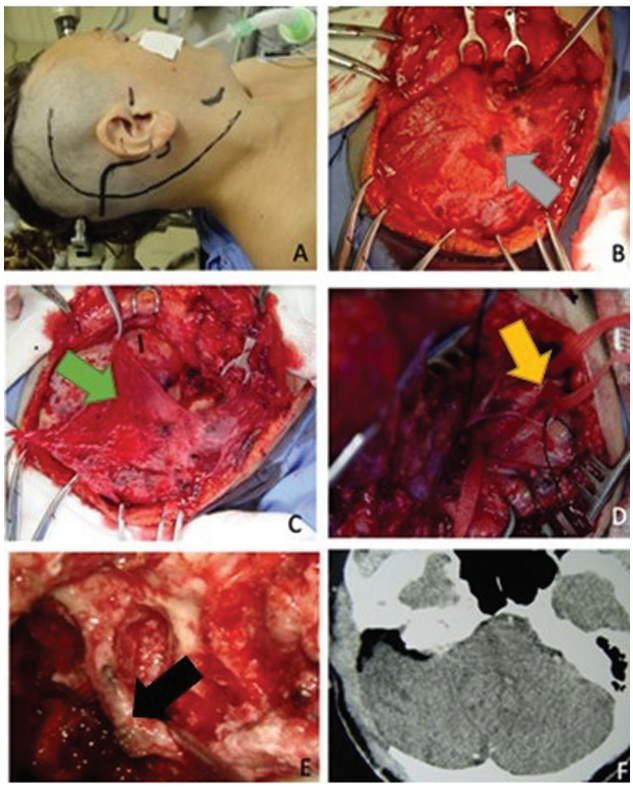

Fig. 5 Case 2, a type C Fisch approach was chosen (A). The temporoparietal fascia and the temporal muscle are identified and individualized for pedicular flap preparation on the preoperatory period (B and C). The cervical neurovascular structures are dissected and individualized for proximal control over the carotid artery (D). After the tumoral resection, a skeletonized intrapetrous carotid artery is observed (E). A CT scan immediately postoperatory, showing a total tumor resection (F). Gray arrow: internal auditory canal. Green arrow: pedicled muscle flap. Yellow arrow: isolated carotid artery. Black arrow: portion of the skeletonized petrous carotid.

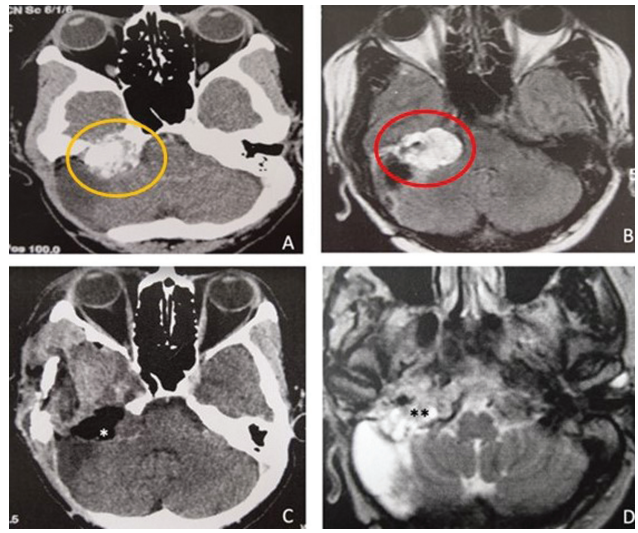

Fig. 6 Case 2, a CT scan with contrast two years after surgery (A) and an axial MRI scan of the T1 with gadolinium (B) revealed a tumoral relapse at the petrous apex, which was resected with a new surgery through the middle fossa approach and anterior necrosectomy. Postoperatory showed tumor resection (C). Three years after the last surgery a new relapse occurs on the jugular tubercle, and the tumor is resected again with another surgery. Nine years after the diagnosis the patient succumbed to the disease due to the metastatic dissemination in both lungs. Yellow arrow: tumor seen on CT scans. Red arrow: tumor seen on MRI scans.

preservation and no signs of recurrence, with follow-ups ranging from 6 months to 8 years.[23]

The translabyrinthine approach, concomitant with the RTA, is required in the cases with labyrinthine invasion, often seen in patients with poor or unserviceable hearing.[23] For patients with unresectable tumors or cases in which surgery was deemed inappropriate, stereotactic radiotherapy (SRS) using gamma knife seems to be useful in the tentative of delaying a tumor growth.[23]

Table 1 Surgical options for EST

Grade	Tumor Extent	Surgical option	Consequence
I	Confined to temporal bone, middle ear cavity, and/or external auditory canal	Retrolabyrinthine-transdural approach	Hearing preservation
II	Extension into posterior fossa	Extended retrolabyrinthine-transdural approach	Hearing preservation
		Approach with labyrinthectomy	Deafness
III	Extension into posterior fossa and middle cranial fossa	Subtemporal craniotomy with petrosectomy	Deafness
IV	Extension to clivus and/or sphenoid wing	Staged anterior and posterior fossa techniques	No mandatory consequences

Note: Adapted from Bambakidis NC, Megerian CA, Ratcheson RA. Differential grade of Endolymphatic Sac Tumor extension by virtue of von Hippel-Lindau disease status. OtolNeurotol. 2004;25:773–81.

Conclusion

The diagnosis of ELST is very difficult, since its early stages present very similar to other more common diseases, such as the Meniere syndrome. Furthermore, the interaction of the ELST and VHL disease results in an even more complicated condition in all terms, represented by its clinical presentation and challenging curative treatment.

Despite this difficulty, early diagnosis increases the chances of successful treatment in terms of hearing preservation, complete tumor resection, and lower mortality rates.

Conflict of Interest

The authors have no conflict of interest to declare.

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