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Pathology in Focus

Endolymphatic sac tumours

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Abstract
Endolymphatic sac tumours (ELST) are rare tumours of the petrous temporal bone. They may arise sporadically or be associated with von Hippel-Lindau disease. Their differential diagnosis is discussed. We present the clinical and histopathological features of two new patients with ELST and outline the management of their condition. In addition, we review a third case previously reported as a choroid plexus papilloma in which the histology has been re-assessed and the diagnosis changed to ELST. The controversy regarding the cellular origins of adenomatous tumours of the temporal bone is highlighted.

Key words: Endolymphatic Sac; Head and Neck Neoplasms; Temporal Bone; Immunohistochemistry

Introduction

The original case of an adenomatous lesion of the petrous temporal bone was described over 100 years ago by Treitel in 1898[1] when he referred to an adenocarcinoma of the middle ear. Today, the cellular origin of ELST is controversial. The cellular origins of all benign glandular tumours of the middle-ear cleft is also contentious. Both states arguably exist through limited understanding of their pathogenesis. This debate is only too apparent when one is aware of the myriad of different terms used to describe them.

A spectrum of pathological labels has been assigned to such tumours in previous years, up to 15 in one review article.[2] Initial attempts at developing a classification system may be traced back to the early 1970s but it was only in 1989 when Heffner[3] proposed that papillary adenocarcinomas of the petrous bone are derived from the endolymphatic sac that a consensus view emerged regarding the origins of invasive adenoid tumours of the petrous bone. However, the notion that previously reported divergent pathologies should be gathered under the sam diagnostic umbrella has been controversial. The diagnosis of ELST is therefore a challenging one with other differential diagnoses discussed later in the text.

Case reports

Case 1

A 50-year-old man presented in 1997 with a history of hearing loss on the right side for 15 years, progressively worsening during the last three years prior to being referred. He also complained of constant tinnitus, otalgia and episodes of unsteadiness, the latter not typical of Ménière's syndrome.

The only positive finding on examination was an abnormal Unterberger's test. Pure tone audiometry revealed a right-sided high frequency sensorineural hearing loss. A computed tomography (CT) scan demonstrated posterior petrous bone destruction by a soft tissue mass. A magnetic resonance image (MRI) scan (without contrast) revealed a destructive lesion which was low signal on T1 and high signal on T2, centred on the endolymphatic sac.

The tumour was removed via the translabyrinthine approach and was brown and cystic in nature. The lesion extended from the middle fossa dura through the labyrinth towards the posterior fossa dura in the region of the endolymphatic sac. The posterior fossa dura adherent to the tumour was excised to achieve total removal. The dural defect was closed with rectus sheath and Tisseel®, with abdominal fat used to close the defect in the temporal bone.

Post-operatively the patient made an uneventful recovery with no neurological deficit suffered other than of a dead ear. Paraffin section histology revealed a papillary tumour (Figure 1) with positive immunohistochemistry for CAM 5.2 (Figure 2 and 3), epithelial-marker antigen (EMA) and glial fibrillary acidic protein (GFAP). This was compatible with the diagnosis of adenocarcinoma of the endolymphatic sac. The patient remains disease-free with no radiological evidence (both CT and MRI) of recurrence after three years.

Case 2

A 68-year-old woman presented in October 2000 with a 15-year history of right-sided pulsatile tinnitus and a right-sided profound sensorineural hearing loss. In the 12 months prior to referral, she complained of worsening

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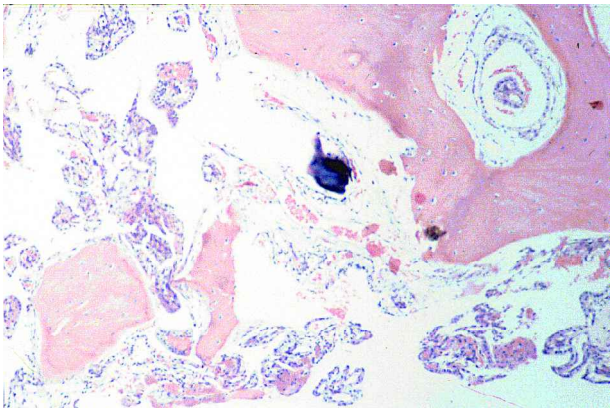

FIG. 1
Case 1. Showing staining of the tumour with papillary pattern within the bone marrow (H&E; ×40).

unsteadiness, paraesthesia in the right mandibular division of the trigeminal nerve and a progressive facial palsy.

A T2-weighted MRI scan showed a 2.7 cm lesion destroying the posterior aspect of the right temporal bone with extension into the cerebellopontine angle (to within 1 mm of the brainstem). A CT scan demonstrated a destructive lesion in the posterior third of the petrous temporal bone eroding the labyrinth with intracranial extension.

A cortical mastoidectomy was performed that confirmed an erosive lesion in the region of the posterior semicircular canal, which bled profusely on biopsy. Histologically this was a low grade papillary adenocarcinoma. The patient was investigated to exclude this being a deposit from a distant primary. Clinical examination of the thyroid and salivary glands, breasts, and abdomen were normal. Furthermore a CT scan of the pelvis and abdomen, a pelvic ultrasound scan, mammography, a chest X-ray, colonoscopy and gastroscopy were all unremarkable.

The patient underwent pre-operative embolization of the supplying vessels (ascending pharyngeal and anterior inferior cerebellar arteries) followed by a translabyrinthine and transcochlear subtotal petrosectomy with an exploration of the posterior cranial fossa. During this procedure the tumour was found to be eroding the labyrinth, cochlea and internal auditory meatus. It extended up to the middle fossa dura and to the jugular bulb and lateral sinus. Tumour was found in the posterior cranial fossa, compressing the brainstem but not adherent to it. Complete tumour

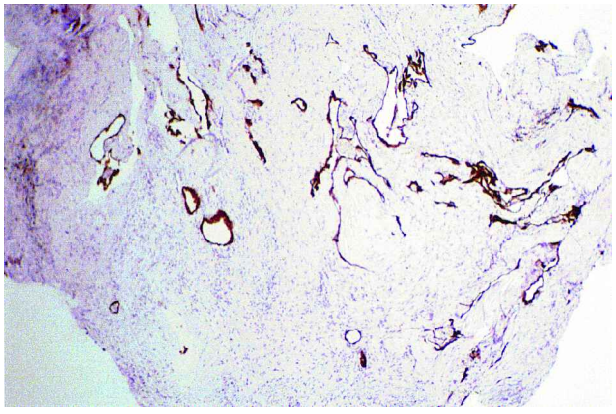

FIG. 2
Case 1. Immunoperoxidase stain for CAM 5.2, a cytokeratin marker, showing marked positivity of the tumour cells within fibrous tissue (×40).

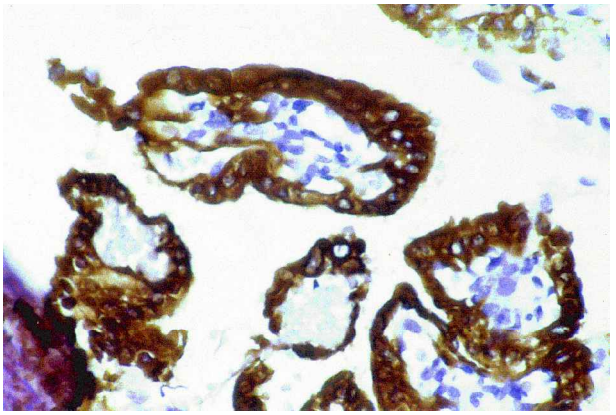

FIG. 3
Case 1. CAM 5.2 positivity in cytoplasm (×250).

removal was achieved, but the facial nerve had to be sacrificed due to tumour invasion in its horizontal portion. Post-operative recovery was uneventful. Follow up at three months showed no clinical evidence of recurrence.

Case 3

This case from the Department of Otolaryngology at the Manchester Royal Infirmary was described in *Skull Base Surgery* in 1992 and was labelled as a choroid plexus papilloma.[4] She was a 24-year-old woman who presented some 10 years ago with a left-sided sensorineural hearing loss and was shown on imaging to have an erosive lesion of the posterior surface of the petrous bone. This was removed through a combined translabyrinthine and retrosigmoid approach. It was a vascular lesion that was mainly confined within the petrous bone but also involved the overlying dura in an *en plaque* manner. After much consideration of the histological picture and consideration of the immunoreactivity – it was reactive to EMA, S100 and GFAP, the diagnosis of choroid plexus papilloma was made. In view of the two new cases described in this article, these specimens were re-examined and the tissue diagnosis changed to ELST. It is of relevance to report that this patient is free of disease nine years after her surgery.

Discussion

Adenoid tumours of the temporal bone are a rarity and with ELST even more so.[5] The origins of these destructive tumours is the subject of much discussion. The terminology applied to adenomatous tumours of the temporal bone is confusing due to the presence of overlapping pathological features.

A detailed study of the anatomy of this region facilitates understanding regarding the histogenesis of these locally invasive tumours of the petrous temporal bone. The inner ear develops from the neural plate with the endolymphatic duct arising from the utriculo-saccular canal. The epithelial lining is of neuroectodermal origin. The middle-ear cleft, however, is formed from the first pharyngeal pouch. Its pseudo-stratified columnar epithelium is by contrast endodermal in type. ELST are therefore classified as being of neuroectodermal origin whereas middle-ear tumours unless they have developed from the ossicular chain or ectopic neuroectoderm are endodermal.[5] These characteristics are used to aid the diagnosis by the employment of immunohistochemical techniques (see later). This does however oversimplify matters as both middle-ear adenomas and paragangliomas demonstrate

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neuroectodermal immunoreactivity. Whether such tumours arise from neural crest cells in the middle ear is yet unanswered.

Hyams and Michaels first referred to benign adenomatous neoplasms (adenoma) of the middle ear in 1976.[6] Their rarity is unchallenged but they appear to be more common than ELST judging by case reports in the medical literature.[7] The discussion of the origins of these middle-ear tumours parallels that of ELST. In their article, Hyams and Michaels[6] present 20 cases of adenomatous tumours of the middle-ear cleft which were studied in detail. All specimens had been received between 1950 and 1970 at the Armed Forces Institute of Pathology, Washington, DC. All patients complained of hearing loss with the variable presence of aural fullness and tinnitus. Their paper states that the tumours were clinically benign with no evidence of metastases and local surgical excision being the treatment of choice. Mean follow-up was 11 years with only one patient death, not attributable to the previous middle-ear pathology. The authors offered the term middle-ear adenoma (MEA) and proposed that the cellular origin of these tumours, based on their histological observations, is a middle-ear mucosal cell. They disregarded suggestions of their contemporaries that such tumours arose from ceruminal glands.[8] All the tumours were localized to the middle ear whilst ceruminal glands are located only in the external auditory meatus. The otoscopic appearance of all external auditory canals had previously been documented as normal. Hyams and Michaels also discounted other published work that primary middle-ear adenomatous tumours were adenocarcinomas. They stated that this fact was not borne out on clinical and histological grounds and suggested the tumours were adenomas, not adenocarcinomas. To highlight this point, six of their own cases thought to be primary adenocarcinomas of the middle-ear cleft were extensively re-examined at the Washington Institute. The original diagnosis was revised in all cases with the tumours being designated as metastatic from sites such as post-nasal space, breast and parotid gland. The clinical characteristics were entirely different from the 20 cases of MEA, with destructive aggressive features being noted. They advocated local surgical excision for MEAs with radical surgery being reserved for cases of adenocarcinoma.

In 1990 a published 27-year review of 13 adenomatous tumours of the middle ear and mastoid stated that two distinctive tumour types exist based on histological and clinical observations.[9] The mixed tumour identified remained localized to the middle-ear cleft whilst the papillary type extended to the petrous apex with intracranial extension commonly being seen. Microscopically an acinic pattern of glandular origin was visualized in the former. In contrast the papillary tumours caused extensive soft tissue and bony invasion but interestingly mitoses were not prominent. The authors hypothesized that the mixed pattern tumour is the previously defined adenoma.[9] The papillary type had frequently been afforded the label of adenocarcinoma by other authors.[2,10] All patients presented with hearing loss, with vertigo and facial palsy being more common in the papillary group.[9] Mixed tumours were seen mainly in males (male to female ratio 7:1), the reverse being true for papillary tumours (female to male ratio 5:1). This delineation into different tumour types is clearly indisputable.

A review article by Kempermann *et al.* neatly outlines the clinical presentation of ELST.[5] Symptoms include sensorineural hearing loss, tinnitus and vertigo with facial palsy also being described. Ataxis is less frequently encountered. The occurrence of Ménière's syndrome varies widely depending on the variable presence of vestibular symptoms – Manski *et al.* reported that eight out of 13 patients diagnosed with ELST suffered vertigo,[11] whilst in other ELST case series, vertigo was surprisingly uncommon.[3] In his paper, Heffner states that there was destruction of some part of the vestibular labyrinth in all the cases he studied. This finding would explain why some patients suffer with vertigo. However, the slow bony erosion allows compensation to occur which may also in part explain why vertigo is not a consistent feature in the history. The initial diagnosis of Ménière's disease only serves to remind us that all patients suffering from these symptoms need full and thorough investigation.[12]

Radiological assessment of these tumours is either by CT or MR scanning. Both reveal enhancement of the non-cystic component with calcification being a constant finding in one series.[13] The tumours are localized at the site of the endolymphatic sac ie. on the posterior surface of the petrous bone half way between the internal acoustic meatus and the lateral sinus. Local bony destruction is a constant finding. Such features are characteristic but not pathognomonic of endolymphatic sac tumours (see differential diagnoses discussed later in the text).

ELST show two main growth patterns. Tumours with a preponderance of colloid filled cavities and sparse stroma may be identified. In these the cysts are usually encapsulated with single layered cuboidal epithelium. Nuclei are isomorphic with mitotic activity rarely seen. In contrast a papillary and dense glandular structure may be found with cystic components seldom present. The stroma has numerous capillaries. Intracellularly, the cytoplasm is clear with a central nucleus.[5]

The diagnosis of ELST also involves immunohistochemical techniques. The immuno-staining reactions of our patients has already been outlined. A review of the literature suggests strong immunoreactivity for cytokeratin and S100, both seen with normal endolymphatic sac tissue.[5] Vimentin is a marker for undifferentiated glial cells which is positive in many cases as is the situation for EMA. Interestingly, positive immunoreactivity is seen with GFAP – previously only associated with glial cells and gliomas. Reactions also occurred with stains for other markers but analysis of the results from different series reveals that no uniform pattern of immunoreactivity exists. Although the positive reactions to the epithelial marker cytokeratin may cause difficulty in differentiating ELST from metastatic disease, other markers may be used to exclude a metastasis. These techniques as yet fail to delineate ELST from middle-ear adenomas as both demonstrate neuroectodermal characteristics.[5]

The differential diagnosis includes metastases from follicular thyroid carcinoma, small cell carcinoma of the lung, renal and breast carcinoma. Other possibilities include paragangliomas and choroid plexus papillomas. As outlined earlier, *Case 3* was initially reported as being a choroid plexus papilloma but after careful review was reclassified as an ELST.[4] Plexus papillomas primarily expand intracranially with no bony erosion. Their histological appearance is less cystic and glandular with a positive immunostaining reaction to transthyretin unlike ELST.[5] Differentiation between some of the aforementioned tumours is extremely difficult on histological grounds. Immunohistochemistry provides one piece of information in complex diagnostic puzzle. It, therefore, cannot be overemphasized that an accurate diagnosis is one which is based on clinical features, radiological assessment, operative findings as well as histological and immunohistochemical results.

Von Hippel-Lindau disease is an autosomal dominant condition which is thought to predispose to ELST. Screening patients with von Hippel-Lindau disease yielded

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an 11 per cent incidence of ELST in one article.[11] Some have called for screening for von Hippel-Lindau disease, the genetic aberration of which is located on the short arm of chromosome 3, in patients with ELST. ELSTs in this condition may be bilateral. However, the case of a patient with bilateral ELSTs with no associated features of von Hippel-Lindau disease has been reported.[14]

The treatment of ELST is surgical with a single stage total microscopic removal usually not achievable in view of the extent of the tumour. The role of adjuvant radiotherapy is as yet undetermined. Tumours grow very slowly and would appear not to metastasize but may recur locally.

The fundamental question as to whether ELST and all papillary adenocarcinomas of the temporal bone are one and the same or different pathological entities is as yet unanswered. Heffner[3] proposed that papillary adenocarcinomas of the petrous bone are indeed of endolymphatic sac origin – he defined the term ELST.

Surprisingly, few patients with ELST present with Ménière's syndrome.[3,5,9] Heffner explains this paradox by arguing that the insidious destruction of the endolymphatic sac system would enable compensation to take place. ELST are epithelial tumours and as such could only have arisen from the endolymphatic sac system or mastoid air cell system given their anatomical location. Given that their site of origin is fairly constant on the posterior surface of the petrous pyramid,[5] Heffner's hypothesis is further strengthened. However, others still argue that papillary adenocarinomas identical to ELST histologically could arise from neuroectodermal tissue in the middle ear (neural crest cells or ectopic deposits).[5] Do ELST represent the malignant transformation of middle-ear adenomas? In their seminal article, Hyams and Michaels[6] made no mention of this.

Conclusion

The diverging nomenclature of previous years is being reclassified. In the light of current evidence, it is reasonable to assume that MEA's are the more confined counterpart of the aggressive papillary primary adenocarcinoma of the petrous temporal bone, this latter tumour being ELSTs. Arguably, advances in immunohistochemistry will ease such deliberations in the future and make this technique the cornerstone of any diagnosis. By contributing to the debate and focusing on the diagnostic pitfalls, it is hoped that greater academic understanding will follow.

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