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Case Report

Clinical experience with the diagnosis and treatment of middle ear adenomatous neuroendocrine tumors

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Abstract: Middle ear adenoma, also known as middle ear adenomatous neuroendocrine tumors (MEANTs), is a rare neoplasm, accounting for < 2% of all middle ear tumors. It is characterized by slow growth, non-invasive behavior, and nonspecific symptoms, which often complicate preoperative diagnosis. This review summarizes our clinical experience in the diagnosis and treatment of 11 cases of MEANT. In this cohort, four cases were preoperatively diagnosed as cholesterol granuloma, five as cholesteatoma, and two as middle ear tumors. The median age at diagnosis was 36.7 years, with all patients (100%) experienced progressive conductive or mixed hearing loss. Additional symptoms included tonal tinnitus (9/11, 81.8%), aural fullness (6/11, 54.5%), otalgia (4/11, 36.4%), pulsatile tinnitus (2/11, 18.2%), otorrhea (2/11, 18.2%), and facial nerve paresis (1/11, 9%). None of the patients exhibited carcinoid syndrome or bloody otorrhea. All patients underwent surgical treatment, and postoperative histopathology confirmed the diagnosis of MEANTs. Immunohistochemical analysis showed positivity for CK and SYN in all cases, S-100 was positive in 91% (10/11) of patients. All patients were followed up for 1.5 to 10 years postoperatively. These findings highlight the nonspecific presentation of middle ear adenoma, which may lead to misdiagnosis as chronic inflammatory disease or other middle ear neoplasms. For differential diagnosis of MEANTs, high-resolution computed tomography (HRCT) of the ear or MRI with non-echo-planar diffusion-weighted imaging (non-EPI DWI) are valuable. Complete surgical resection remains the mainstay of treatment, and ossicular chain reconstruction should be considered when appropriate.

Keywords: Middle ear adenomatous neuroendocrine tumor, superficial parotidectomy, endocrine

Introduction

In 1976, Hyams and Michaels first proposed the concept of middle ear adenoma, a rare neoplasm accounting for less than 2% of all middle ear tumors. Owing to their mixed neuroendocrine and adenomatous histologic features, these tumors have been described using various terms, including middle ear adenoma, middle ear carcinoid tumor, and middle ear adenomatous neuroendocrine tumor (MEANT). Middle ear adenoma are characterized by slow growth, non-invasive behavior, and nonspecific symptoms, which contribute to diagnostic difficulty [1-3].

In 2018, Marinelli et al. [4] proposed a TNMS staging system. Based on TNMS stage, different surgical approaches were recommended, including canal wall-up mastoidectomy, mastoidectomy and tympanoplasty, lateral temporal bone resection, and/or superficial parotidectomy. This study summarizes our clinical experience in the diagnosis and treatment of MEANTs, alongside a review of relevant literature, aiming to provide insight into optimal diagnostic strategies, surgical management, and long-term follow-up.

Patients and methods

This retrospective study included patients diagnosed with middle ear adenomatous neuroendocrine tumors at the Department of Otolaryngology-Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University. Clinical data, including temporal bone CT and MRI findings (MRI was not available in some cases due

to historical limitations), intraoperative findings, and histopathologic reports, were retrieved from the institutional medical record system and surgical archives between January 2004 and September 2023.

No prospective recruitment, additional clinical interventions, imaging examinations, tissue sampling, or questionnaires were performed specifically for this study. The study protocol was reviewed and approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (approval ID: TREC2024-KYS138). Due to the retrospective design of this study, the requirement for written informed consent was waived. All data were anonymized prior to analysis. Patient identifiers (including name, medical record number, date of birth, and any potentially identifiable intraoperative images) were removed before data processing, and investigators did not retain access to directly identifiable personal information after data extraction.

Patient presentation

The clinical manifestations of patients are summarized in **Table 1**. Cases 1-10 underwent primary surgery at our institution, whereas Case 11 presented with aural fullness and intermittent otalgia two years after an initial surgery performed elsewhere, during which a diagnosis of chronic otitis media was made. All patients (100%) presented with progressive conductive or mixed hearing loss. Additional symptoms included tonal tinnitus (9/11, 81.8%), aural fullness (6/11, 54.5%), otalgia (4/11, 36.4%), pulsatile tinnitus (2/11, 18.2%), otorrhea (2/11, 18.2%), and facial nerve paresis (1/11, 9%). None of the patients exhibited carcinoid syndrome or bloody otorrhea.

The most common otoscopic finding was an intact tympanic membrane with a red, pink, or pale bulging mass (4/11, 36.4%). Perforation of the eardrum with extension into the external auditory canal (EAC) was observed in another 36.4% (4/11) of cases. Imaging revealed soft-tissue density masses in the tympanum in all cases, with ossicular chain involvement identified in 8 patients (8/11, 72.7%). Tumor staging included one case of T1N0M0, four cases of T2aN0M0, one case of T2bN0M0, four cases of T2cN0M0, and one case of T3N0M0. The diagnosis was established following the 2022 WHO classification criteria, based on both architectural patterns and immunohistochemical profiles [5].

Treatment and surgical procedure

The surgical approach, tumor stage, intraoperative findings, biopsy results, and immunohistochemical profiles of all 11 cases are summarized in **Table 2**. Except for Cases 2, 6 and 7, the incus was removed intraoperatively in all patients. For these three cases, the ossicular chains were not involved by the tumor; therefore, only tympanotomy with exploration was performed.

In Case 3, intraoperative findings revealed incomplete bony coverage of the tympanic segment of the facial nerve. Given the preoperative facial nerve paralysis, facial nerve decompression was performed. Case 11 had undergone left middle ear surgery two years earlier, during which the incus and part of the malleus were removed, while the stapes was preserved and covered with cartilage. During revision surgery, mastoidectomy and tympanoplasty were performed; however, ossicular chain reconstruction was not performed. Intro-operative images of Case 1 are shown in **Figure 1**.

All patients had postoperative pathologic findings consistent with MEANT. Immunohistochemical results are summarized in **Table 2**. All patients were followed up for 1.5 to 10 years postoperatively. Case 6 experienced recurrence of otorrhea and hearing loss 8 years after initial surgery and underwent revision surgery. Postoperative pathology confirmed recurrent MEANTs, and the patient has remained symptom-free thereafter. Case 11 underwent a second operation during the study period, with postoperative pathology confirming MEANTs. However, the absence of histopathological data from the first surgery precluded confirmation of whether this was a recurrence. No recurrence was observed in the remaining patients during follow-up to date.

Discussion

Middle ear adenoma is typically nonspecific, lacking well-defined diagnostic criteria. The exact pathogenesis of MEANs remains unclear. Unlike typical neuroendocrine tumors in other organs, MEANs rarely exhibit common ontoge-

Table 1. Patient information and clinical characteristics of selected cases

Case	Sex	Age	Symptom	Physical Sign	CT Imaging	MRI Imaging	Proposed Diagnosis
1	F	25	CHL, TT, AF	Intact TM with obscured landmarks	STS in the TC, partially enveloping the OC	Isointense T1- and T2- weighted images; no obvious hyperintensity on DWI, heterogeneous and significant enhancement	cholesterol granuloma
2	F	32	CHL, TT, vertigo	Intact TM, with visible mass in TC	STS in TC, partially enveloping OC and obscuring the OW	Slightly hyperintense on T1- weighted images and isointense to slightly hypointense T2-weighted images; no obvious diffusion restriction; significant enhancement	tumor, uncertain
3	F	48	Otalgia, MHL, PT, FNP	Perforation of pars tensa with granulation tissue protruding into EAC	STS in TC and mastoid extending into EAC and enveloping OC; incomplete bony facial nerve canal	Isointense T1 and slightly hyperintense T2 signals with significant enhancement; enhancement of tympanic segment of facial nerve	cholesteatoma
4	M	33	CHL, TT, AF	Intact red bulging TM	STS in TC and mastoid extending into EAC and enveloping OC	Hyperintense T1 and hypointense T2 signals in middle ear and mastoid region; isointense T1 and T2 signals in TC with heterogeneous enhancement	inflammatory granuloma
5	M	32	MHL, TT, Otalgia, Otorrhea	Pink mass visible in left EAC	Similar to Case 4	Similar to Case 1	tumor, uncertain
6	M	21	CHL, TT	Posterior superior quadrant TM bulging outward	STS in TC and mastoid enveloping OC	T1 low or isointense; T2 high or isointense signals in tympanum; mild enhancement	cholesterol granuloma
7	M	28	MHL, Otalgia, TT, AF	Red bulged TM	Similar to Case 6	MRI not available	cholesteatoma
8	F	52	CHL, AF, PT	Red bulged TM	Similar to Case 6	Hypointense T1, hyperintense T2 signals; low signal on DWI; poorly defined margins with enhancement	tumor, uncertain
9	F	40	CHL, TT, AF	Pale mass in EAC; TM not visible	STS in deep EAC and TC	MRI not available	cholesteatoma
10	F	49	CHL, TT	Intact TM	Ossicles surrounded by STS with clear boundary in TC	Isointense T1 and slightly hyperintense T2 signals; heterogeneous enhancement	cholesteatoma
11	M	44	AF, Otalgia, MHL, TT	Mass in left EAC	Patchy STS in TC and EAC; OC poorly visualized	MRI not available	cholesterol granuloma

CHL, conductive hearing loss; MHL, mixed hearing loss; AF, aural fullness; TT, tonal tinnitus; PT, pulsatile tinnitus; FNP, facial nerve paralysis; TM, tympanic membrane; STS, Soft tissue shadows; TC, tympanic cavity; EAC, external auditory canal; OC, ossicular chain; OW, oval window.

Table 2. Treatments, TNM, frozen biopsy, and pathologic immunohistochemical results of this cohort

Case	Treatments	TNMS	Frozen Biopsy	CK	SYN	NSE	CD56	S-100	Ki-67	CgA	P53	Vim
1	oto-endoscopy; endaural incision; tumor resection + TM + incus removal	T2aN0M0	MENTs	+	+	-	+	-	1%	-	-	-
2	microscopy; postauricular incision; tumor resection + TM with intact ossicles	T2aN0M0	MENTs	+	+	-	-	-	-	-	-	-
3	microscopy; postauricular incision; tumor resection + CWD mastoidectomy + TM + incus removal + facial nerve decompression + postauricular lymph node dissection	T3N0M0	low grade malignant tumor	+	+	+	+	-	10%	-	+	-
4	microscopy; postauricular incision; tumor resection + CWD mastoidectomy + TM + incus removal	T2cN0M0	low grade malignant tumor, more likely MENTs	+	+	+	-	+	2%	partial +	-	+
5	microscopy; postauricular incision; tumor resection + CWU mastoidectomy TM + incus removal	T2cN0M0	MENTs	+	+	partial +	+	-	1%	partial +	-	+
6	microscopy; postauricular incision; tumor resection + TM with intact ossicles	T1N0M0	MENTs	+	+	+	-	-	5%	-	-	+
7	microscopy; postauricular incision; tumor resection + CWU mastoidectomy + TM with intact ossicles	T2aN0M0	MENTs	+	+	-	+	-	5%	+	-	+
8	microscopy; postauricular incision; tumor resection + CWU mastoidectomy + TM + PROP	T2bN0M0	glomus tympanicum tumor	+	+	+	-	-	1%	-	-	+
9	microscopy; postauricular incision; tumor resection + TM + incus removal	T2cN0M0	glomus tympanicum tumor	+	+	+	+	-	3%	+	-	-
10	microscopy; preauricular and endaural incisions; tumor resection + TM with intact ossicles	T2aN0M0	Note applied	+	+	-	-	-	-	-	+	+
11	microscopy; postauricular incision; tumor resection + CWU mastoidectomy + TM	T2cN0M0	Note applied	+	+	-	+	-	-	-	-	-

TM, tympanoplasty; CWD, canal wall-down; CWU, canal wall-up; T, tympanotomy; PROP, partial ossicular replacement prosthesis; no intraoperative frozen biopsy was submitted for cases 10 and 11. +: positive; -: negative.

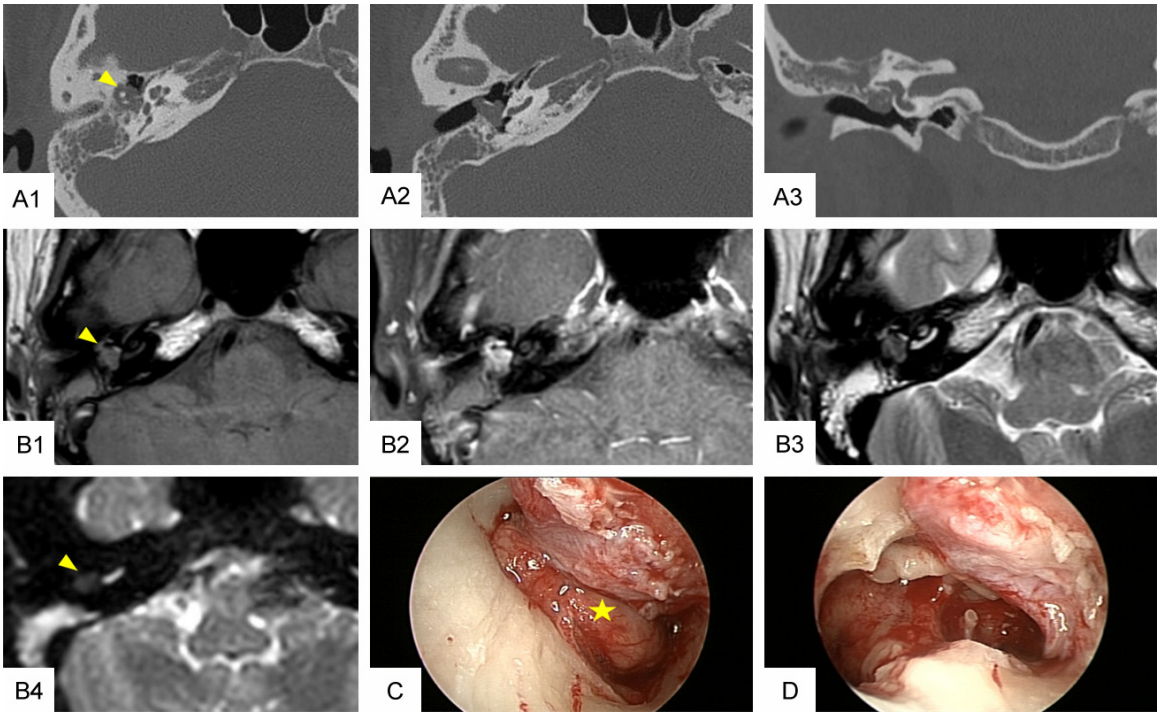

Figure 1. Intra-operative images of case 1. Soft-tissue density (yellow arrow) was observed in the tympanic cavity (TC), enveloping the ossicular chain on CT (A1, A2: axial; A3: coronal). MRI demonstrated isointense signals on both T1- and T2-weighted images (B1, B3), heterogeneous enhancement (B2), and no obvious diffusion restriction on DWI (B4). (C and D) show intra-operative endoscopic images, in which the tumor is indicated by a yellow asterisk.

netic mutations associated with aggressive carcinoma, which is consistent with their generally indolent clinical behavior [6].

Preoperative imaging helps differentiate MEANTs from other middle ear diseases and allows for precise evaluation of tumor extent and its anatomic relationship to adjacent structures [7]. On MRI, MEANTs typically demonstrate isointense or slightly hyperintense signals relative to white matter on T1-weighted images, with clear contrast enhancement. On T2-weighted images, their signal intensity is usually intermediate to slightly hyperintense, approaching that of gray matter. In contrast, otitis media, cholesteatoma, or cholesterol granulomas generally do not show significant enhancement patterns [8].

In this study, most patients who underwent MRI imaging demonstrated isointense signals on T1- and T2-weighted MRI, with evidence of heterogeneous enhancement (**Table 1**). Notably, no diffusion restriction was observed on DWI, a finding indicative of middle ear adenoma or other neoplastic lesions. In addition, glomus tympanicum, the most common primary middle ear tumor, shares the imaging feature of contrast enhancement with MEANTS, leading to potential misdiagnosis. In this study, two cases were initially misdiagnosed as glomus tympanicum. However, glomus tympanicum typically presents with distinct clinical features (e.g., pulsatile tinnitus) and may demonstrate a vascular blush on angiography, which can aid in differentiation. From a pathologic perspective, differentiation between MEANs and cholesteatoma relies on distinct immunophenotypic profiles. Cholesteatoma is characterized by keratinizing squamous epithelium with positivity for high-molecular-weight cytokeratins, whereas MEANs exhibit glandular and neuroendocrine differentiation, with expression of markers SYN and CgA. In addition, the absence of CD68-positive macrophage infiltration also helps distinguish MEANs from cholesterol granuloma, which is primarily an inflammatory reaction to cholesterol crystal deposition.

To date, no standardized treatment guidelines have been established for MEANTs. Surgical approaches remain heterogeneous. Complete surgical resection is considered the corner-

stone for MEANTs, whereas simple tumor excision or tympanic exploration is not recommended for MEANTs at any TNM stage [9]. MEANTs may demonstrate local aggressiveness. Distant metastasis is rare; therefore, long-term follow-up is essential. In our cohort, Case 6 experienced recurrence seven years after initial surgery, and Case 11 was suspected of recurrence at presentation to our center. Notably, Case 6 exhibited a Ki-67 index of 5%, which is slightly higher than that reported in many previously published MEANT cases [10]. Although many reported MEANTs demonstrate a low proliferative index (Ki-67 values < 3%), higher values have also been reported, and the prognostic significance of Ki-67 in MEANTs remains incompletely understood.

This study has several limitations. Due to the extreme rarity of MEANTs and the retrospective design of this single-center study, fresh tissue samples were unavailable, limiting further molecular analyses such as transcriptomics or proteomics to identify potential driver mutations or dysregulated signaling pathways. Furthermore, the small cohort size (n = 11) precluded statistical modeling to determine correlation between IHC markers and recurrence risks. Furthermore, due to the retrospective nature of the study and the long study period, standardized quality-of-life assessments and long-term hearing outcome data were not consistently available in earlier medical records. Although recurrence was observed, the overall event rate remained very low. Consequently, the assessment of prognosis was primarily focused on recurrence rates and symptom relief. Future prospective, multicenter studies with standardized functional outcome measures and extended follow-up are warranted to better define the prognostic landscape of MEANTs.

Conclusion

Presentation of middle ear adenoma is typically nonspecific and may be easily misdiagnosed as chronic inflammatory disease or other middle ear tumors. HRCT of the temporal bone and MRI with a non-EPI-DWI are valuable for differential diagnosis of MEANTs. Complete surgical resection remains the mainstay of treatment, and ossicular chain management can be performed when appropriate. Immunohistochemical evaluation is essential for definitive diagnosis of MENT. Long-term follow-up is recommended to monitor for recurrence.

Disclosure of conflict of interest

None.

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