Middle Ear Neuroendocrine Tumors: A Case Series Highlighting Diagnostic and Management Challenges

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Introduction

Middle ear neuroendocrine tumors (MeNETs) represent <2% of middle and inner ear neoplasms.[1] First described as adenomas by Hyams and Michaels in 1976[2] and later termed carcinoid tumors by Murphy et al. in 1980,[3] these lesions remain a source of debate in terminology and biological behavior. The World Health Organization now recognizes "MeNET" as the preferred term, reflecting their dual epithelial and neuroendocrine nature.[4] Clinical presentation is nonspecific, with hearing loss, tinnitus, and otalgia mimicking more common middle ear disease. Imaging is also limited, typically showing middle ear opacification without distinctive features.[5] Definitive diagnosis therefore relies on histopathology and immunohistochemistry (IHC), with frequent expression of cytokeratins, synaptophysin, and chromogranin.[1,6] Marinelli et al. proposed a T/N/M/S staging system that stratifies tumors by extent, nodal or metastatic disease, and secretory status, offering a framework for prognosis.[7]

Methods and Materials

This retrospective multi-institutional case series was performed at two tertiary academic referral centers: UC Davis Medical Center and Harborview Medical Center. Five patients with pathologically confirmed MeNETs were included. Clinical data were extracted from electronic medical records and included demographics, presenting symptoms, imaging, operative findings, pathology, and follow-up. All histologic slides were reviewed at participating institutions to confirm the diagnosis. Hematoxylin and eosin staining was performed, and immunohistochemical analysis was used to assess for neuroendocrine differentiation. Markers included AE1/AE3, CAM5.2, synaptophysin, chromogranin, vimentin, Ki-67, and others as indicated. The study was conducted under IRB approval (UC Davis #2187227-1).

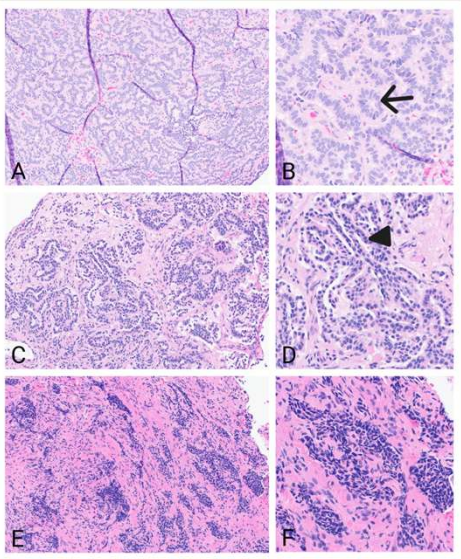

Figure 1. Morphologic patterns in MeNETs: ribbon-like/rosette architecture (arrows), glandular structures with lumina (arrowheads), and solid growth of small round cells. Images from patients 2 and 3, stained with H&E.

Table 1. Clinical Characteristics and Recurrence of Middle Ear Neuroendocrine Tumors in Five Patients

Case	Age and Sex	Initial clinical symptoms	Primary Site	Recurrence (yes/no)	Recurrence Symptoms	Interval to Recurrence	Surgical History
1	14 F	Hearing loss, tinnitus, otalgia, vertigo	Posterior-superior middle ear, attic, antrum	Yes	Hearing loss, otorrhea, tinnitus, drainage	14 years	Primary, second look, recurrence, revision for residual tumor, second look
2	32 F	Hearing loss, otalgia	Middle ear, mastoid, EAC, incus	Yes	Otalgia, imbalance, headaches	3 years	Primary, recurrence, second look
3	65 F	Hearing loss, ear fullness	Middle ear, ossicles, attic, mastoid	No	N/A	N/A	Primary, revision for residual tumor, second look
4	36 F	Hearing loss, tinnitus, ear fullness	Middle ear, ossicles	No	N/A	N/A	Primary, second look
5	49 F	Hearing loss, tinnitus, ear fullness, vertigo	Temporal bone, middle ear, ossicles, IAC	No	N/A	N/A	Primary, revision surgery for residual tumor

Results

The cohort included five patients (three female), mean age 39 years (range 14–65). All presented with unilateral middle ear symptoms, most commonly hearing loss, followed by tinnitus, aural fullness, vertigo, and otalgia. Ossicular involvement was universal, with stapes adherence in all cases and incus necrosis in three. All underwent tympanomastoidectomy, and each required at least one revision procedure for residual disease, recurrence, or second-look. Two patients experienced histologically confirmed recurrences at 3 and 14 years, underscoring the potential for delayed relapse.

Immunohistochemistry demonstrated synaptophysin positivity in all tumors and chromogranin positivity in four, while S100 was negative in every case, excluding paraganglioma a common histologic mimic.[8] When staged according to the Marinelli T/N/M/S system, four patients were T2 (both of the recurrences) and one was T4. These findings highlight that even lower graded T2–T3 tumors carry a notable risk of recurrence, supporting the role of staging in guiding surgical planning and long-term surveillance.[7]

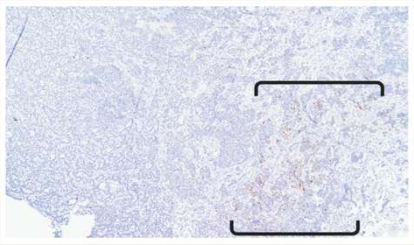

Figure 2. High-power image of patient 3's biopsy showing focal chromogranin staining (brackets). Chromogranin expression in MeNETs is often limited, variably distributed, and may appear weak or absent.

Discussion

MeNETs present unique diagnostic and therapeutic challenges. Clinically and radiographically, they are often indistinguishable from cholesteatoma or other middle ear masses.[5] Histopathology with IHC remains the diagnostic gold standard, typically showing uniform cuboidal cells in trabecular or glandular arrangements, with positivity for pancytokeratin, synaptophysin, and chromogranin.[1,6] Negative S100 staining further differentiates MeNETs from paragangliomas.[8] Surgery is the cornerstone of management. Canal wall up procedures may be sufficient for localized tumors, while canal wall down tympanomastoidectomy or subtotal petrosectomy may be required for recurrent or extensive disease.[9] Radiation has a limited role and is generally reserved for unresectable residual disease.[9,10] In our series, recurrences occurred in two patients, including one 14 years after initial surgery. Notably, tympanic membrane involvement was present in 3 patients (60%), and both recurrences arose in this subset, suggesting that TM adherence may predispose to residual disease and should encourage the surgeons for a wider resection of the tympanic membrane, and may add new insight into Marinelli's staging system. [7]

Conclusion

MeNETs are rare, low-grade tumors with variable clinical behavior. Diagnosis requires thorough histopathologic and immunohistochemical evaluation. Surgery remains the mainstay of treatment, but recurrence is frequent, often years after initial surgery. Our findings emphasize the importance of individualized surgical management, planned second-look procedures, and long-term imaging surveillance. The association between tympanic membrane involvement and recurrence in our series may represent a staging refinement opportunity. Multidisciplinary collaboration is critical, and multicenter prospective studies are needed to refine treatment guidelines and surveillance strategies .

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