INTRODUCTION

Neuroendocrine tumors are infrequent causes of middle ear masses. Previously divided into middle ear adenoma, and carcinoid tumor of the middle ear, but now seen as stages of the same tumor: Neuroendocrine adenoma of the middle ear (NEAME).\textsuperscript{1-4} They have an indolent clinical course with unspecific symptoms, \textit{for example}, compromised hearing, ear fullness, tightness, and dizziness without nystagmus. Alternative diagnoses include benign and malignant conditions, \textit{for example}, cholesteatoma, glomus tympanicum, jugulotympanic paraganglioma, acoustic neuroma, meningioma, endolymphatic sac papillary tumor, and adenocarcinoma. Preoperative diagnostics (based on clinical findings) with CT or MRI show an opacity without bone destruction. At surgery, a whitish or yellowish brown, elastic mass is seen. Histopathology reveals a glandular to trabecular tumor, immunopositive for chromogranin, synaptophysin, or cytokeratin-20. In a study of 94 cases, Saliba and Evrard proposed a classification of NEAME based on immunohistochemistry and presence of metastases.\textsuperscript{2} Marinelli \textit{et al} proposed a T/N/M/S staging system in a retrospective study with 32 cases.\textsuperscript{4}

Treatment aims at R0 resection by tympanotomy, radical mastoidectomy, or subtotal petrosectomy for total removal of the lesion and the involved ossicular chain.\textsuperscript{2} The effect of radiotherapy is unclear.\textsuperscript{2,4}

Previously, these lesions were thought to be benign, but local recurrences, metastases to cervical lymph nodes, the parotid, bone, and viscera are described, sometimes many years postoperatively.\textsuperscript{1,2,4,5}

CASE REPORTS

Three cases of NEAME were operated at our department (catchment area 300,000 inhabitants) and two cases at collaborating units (catchment area 280,000 inhabitants) during a four years period. During that period, we resected about 15 middle ear tumors (excluding cholesteatoma) at our department. These five cases are described to show the clinical variation and the importance of raised attention among clinicians for proper diagnosis.

2.1 Case 1

A male (57 years) with 10 years history of dizzy spells and left aural fullness. A mass in the left hypotympanum with intact eardrum was seen together with conductive hearing loss. The HINTS (head impulse, nystagmus, and test of skew) examination was negative. Videonystagmography, auditory brainstem responses and brain MRI were normal. CT showed a mass in the left middle ear without bone...
At exploration, a dark yellowish to brown mass in the hypo- and protympanum was found and radically excised (Figure 1). Histopathology showed a trabecular to glandular neuroendocrine neoplasia, immunopositive for cytokeratin AE1/3, chromogranin A and vimentin, while negative for S100, CK5/6, and TTF1. Ki67-index was <2%, and the finding is compatible with NEAME according to Saliba’s classification and T1 with Marinelli’s staging system (Tab). The diagnosis of this and the following cases was corroborated at the University Hospital by a pathologist with extensive scientific and clinical experience in neuroendocrine tumors.

Seven years of follow-up with clinical examinations, audiograms, and CT scans show no evidence of recurrent disease.

### 2.2 Case 2

A female (36 years) had six months of dizzy spells (sometimes position dependent) and a greyish yellow mass behind intact eardrum. CT scan showed a mass surrounding the ossicles (Figure 2).

Audiogram was normal without air-bone gap (ABG). The mass was excised through retroauricular exploration with preservation of the ossicular chain. Radicality was hard to confirm in the sinus tympani, but postoperative CT showed no abnormality except one densified retrofacial cell (intact bone). With the experience from case 1, NEAME was suspected already at surgery (Figure 2, Video S1) and histopathology later confirmed this, stage T2a (Table 1).

Follow-up during seven years shows an unchanged densified retrofacial cell and aerated middle ear.

### 2.3 Case 3

A female (41 years) had right aural fullness, normal otoscopy but minor (10-15db) ABG. Valsalva maneuvers were recommended but she returned after three years without improvement of symptoms or ABG. A mass behind the upper half of the intact eardrum was now noted. A CT scan revealed an opacity expanding into the attic and mastoid cavity (Figure 3).
Through a right postauricular attico-antrum-mastoidectomy (canal wall-up technique) with extended facial recess approach, a fibrotic, multilobulated dark yellow-gray tumor was observed in the upper part of the mesotympanum and the attic, expanding into the antrum. The ossicles were embedded but not eroded. The facial nerve was intact. The incus and hammerhead were removed, the tensor tympani tendon was cut, and the tumor was macroscopically totally excised even from the anterior attic where it was growing around the facial nerve (Figure 3).

Histopathology agreed with NEAME, stage T2b (Tab). As the patient had unspecific bowel symptoms, a potential metastatic intestinal neuroendocrine tumor was ruled out by abdominal CT, endoscopy and urinary 5-HIAA. Follow-up during four years shows no signs of recurrence.

### 2.4 Case 4

A female (40 years) had signs of right chronic otitis but developed facial nerve palsy. Otoscopy showed eardrum-perforation, a polyp, discharge, and granulation tissue. CT scan revealed opacity in the middle ear and the mastoid. Biopsy from the mass showed NEAME and attico-antrum mastoidectomy was performed. The ossicles were removed, the posterior tympanum was involved, and radicality was hard to estimate. Histopathology showed NEAME, stage T3 (Tab).

Postoperatively, the facial nerve fully recovered. Follow-up, including $^{68}$Ga-DOTATATE-PET/CT, has revealed signs of recurrence. New surgery is planned.

### 2.5 Case 5

A man (38 years) with conductive hearing loss had a mass in the right middle ear with intact eardrum. CT showed an opacity in the middle ear and a cholesteatoma was suspected.

At explorative tympanotomy, a yellowish distensible tumor was biopsied and immunohistochemistry showed NEAME (Tab). A R0 resection could be performed 2018 and to date no recurrence is seen.

### 3 DISCUSSION

The knowledge on NEAME is still limited with few published cases and scarce recognition among practitioners. This series of five patients detected during a short period in

| TABLE 1 Immunohistochemical Data and Classification of Reported Cases |
|---------------------------------------------------------------|
| Case 1 | + | + | <2% | ++ | - | - | NEAME | T1 |
| Case 2 | + | - | ++ | <2% | - | NEAME | T2a |
| Case 3 | + | + | 2-3% | (+) | + | NEAME | T2b |
| Case 4 | + | + | <2% | - | + | NEAME | T3 |
| Case 5 | + | + | + | <2% | - | NEAME | ? |

Note: AE 1/3 = antibody cocktail binding to cytokeratin 1-8, 10, 14-16 and 19; Cg A = Chromogranin A; Syn = Synaptophysin; MNF116 = monoclonal cytokeratin antibody MNF116; Ki-67 = Ki-67 labeling index; S100 = Protein S100; CK 5/6 = Cytokeratin 5/6.

**FIGURE 3** Tumor is seen in the upper part of the right middle ear. The incus (arrow) is seen embedded in the tumor. Inset shows CT scan of temporal bone with mass in the superior part of the right middle ear, in the antrum and mastoid.
a small catchment area indicate that experience of this condition facilitates proper identification and treatment.

The Saliba and Marinelli classifications were utilized for our cases as detailed in Table showing T1, T2a, T2b, and T3 tumors but only N0/M0/S0.

Treatment aims at surgical R0 resection with preservation of function, if possible. Adjuvant treatment is not recommended but long-term follow-up (sometimes life-long) is recommended due to slow progression and difficulty to resect with wide margins. Clinical examination and CT/MRI are the mainstay for early detection while $^{68}$Ga-DOTATATE-PET/CT awaits further studies.\textsuperscript{1,2,4,5}

4 | CONCLUSION

Despite its rarity, NEAME is a differential diagnosis in middle ear disease. This study highlights that more cases can be detected with an increased awareness through education and personal experience. Early radical surgery entails good prognosis, but long-term follow-up is warranted.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

PBR: performed the surgery of the first three cases, collected all data and obtained consent from the patients. BW: has been consulted as a specialist in neuroendocrine tumors. Together PBR and BW designed the paper, contributed in writing the paper, and approved the final version of the manuscript.

ETHICAL APPROVAL

According to Swedish law, an ethical approval is not demanded for publication of this kind of case report where the patients have received established treatment. This was recently corroborated by a higher court “The Ethics Review Appeals Board.” All the patients gave consent to the publication of the cases.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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