Neuroendocrine Neoplasms of the Ear

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Received: 21 February 2018 / Accepted: 23 April 2018 / Published online: 1 August 2018
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Abstract

Neuroendocrine neoplasms of the ear are uncommon primary tumors. There is a reported debate in the literature as to the true nature of these tumors and how to classify them. However, there is a kind of consensus that they can represent a spectrum of a common entity with dual glandular and neuroendocrine differentiation. The differential diagnosis of these tumors is broad but their morphologic, immunohistochemical, and radiographic features help to differentiate them from other entities. The tumors have mostly bland histology and indolent biological behavior, yet they may recur and metastasize. It is important to accurately recognize these tumors in order to perform the right management and limit their morbidity. In this article, we review the pathogenesis, histology, immunohistochemical features of neuroendocrine neoplasms of the ear and we discuss their differential diagnosis, clinical behavior and management.

Keywords Neuroendocrine neoplasms · Middle ear · Middle ear adenoma · Carcinoid

Introduction

Neuroendocrine neoplasms of the ear (NENE) are uncommon neoplasms, accounting for <2% of primary ear tumors. They exhibit histologic and immunohistochemical evidence of dual neuroendocrine and glandular differentiation [15]. Hyams and Michaels were the first to report these tumors in 1976, describing 20 middle ear glandular neoplasms that did not resemble paraganglioma or salivary gland tumors, designating them as middle ear adenomas [8]. In 1980, Murphy et al. reported a similar middle ear tumor that showed ultrastructural and histochemical neuroendocrine features, labeling it carcinoid [9]. Since then, several cases of middle ear adenomatous/neuroendocrine tumors have been reported but mostly limited to case reports and small series [4, 12]. These tumors have been described by many names, including middle ear adenoma, carcinoid, adenomatous tumors, adenocarcinoid, and amphicrine tumor. However, the commonality of these tumors is the presence of both glandular/epithelial and neuroendocrine elements. This dual differentiation is supported by immunohistochemistry which shows two distinct staining patterns, one for CK7 and another for

neuroendocrine markers. The common phenotype and the similar characteristics of these tumors suggest that they can represent a spectrum of one entity; therefore there is a tendency to unify them under the name of middle ear adenoma. These tumors have mostly bland histology and indolent biological behavior with slow local growth. However, aggressive histologic patterns and metastases have been reported [4]. In this manuscript, we discuss different aspects of NENE including pathogenesis, histologic and immunohistochemical features, diagnosis, clinical behavior, and treatment.

Pathogenesis

The pathogenesis of NENE is not clear yet. Hyams and Michaels postulated that these tumors originate from the middle ear mucosa [11]. It has been also suggested that they may originate from displaced or entrapped embryonic rests of glandular cells in the middle ear mucosa [11] and some authors have advocated that these embryonic cells are neural-crest derived stem cells [4]. Another potential explanation, proposed by Thompson and Torske, is that middle ear neuroendocrine tumors originate from an undifferentiated pluripotential endodermal stem since epithelial cells with neuroendocrine differentiation do not exist in this location [14].

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Tumors Classification

Given the dual endocrine and exocrine differentiation of NENE, different classifications have been used to describe these neoplasms. However, to date, there is no standard classification system of NENE that has been accepted in the literature, especially that these tumors can have endocrine and exocrine differentiation. The analogy between middle ear adenoma and carcinoid or low grade neuroendocrine seems disputable. While Ramsey et al. have concluded that they are two distinct biologic neoplasms [12], Torske and Thompson have suggested that they both represent the same tumor [14]. Recently, based on the expression of the detection of the immunohistochemical markers and the presence of metastases, Saliba et al. have proposed to classify the middle ear glandular tumors into three types (Saliba's classifications of middle ear glandular neoplasms). The most common type is type I, accounting for 76% of cases, and is the neuroendocrine adenoma of the middle ear which shows positive immunohistochemical markers and negative metastases. Type II is the middle ear adenoma, which was found in 20% of cases, and exhibits negative immunohistochemical markers and negative metastases. The least common, type III (4%), is the carcinoid tumor, which shows positive immunohistochemical markers and positive metastases and/or carcinoid syndrome [13]. This classification identifies that up 12.7% of patients with type I tumors may develop recurrences or metastases [4]. Despite the reported debate in the literature as to the true nature of these tumors, there is a kind of consensus that they can represent a spectrum of a common entity with different degrees of glandular and neuroendocrine differentiation; moreover, there is a tendency to unify them under the term middle ear adenoma. In fact, these tumors are listed under the term middle ear adenoma in the WHO of 2017, stating that it is still appropriate to refer to them as adenomas with neuroendocrine features [7].

Clinical Features

Tumor usually presents as a nonspecific ear mass. It has been reported in a wide patient age range with an average age of 50 years old. There is no gender preference noted. The most common presenting symptom is unilateral conductive hearing loss, found in 86% of patients [11]. Other reported symptoms include ear fullness, tinnitus, and dizziness. Facial nerve paralysis, otic discharge and pain rarely occur and they may be indicative of malignancy [15]. Otoscopic examination typically reveals intact tympanic membrane with tumor confined to the middle

ear space with possible extension to the mastoid. Occasionally, the tumor can perforate the tympanic membrane and extends into the external auditory canal [15]. Radiographically, on CT, tumor appears as an avascular soft tissue density within the mastoid bone. Bone expansion within the middle ear space is common, associated with bone remodeling and encasement of the ossicles, but usually without bone destruction [4]. MRI may be useful in cases with extension to the posterior fossa [6]. On MRI, tumors are isointense to hyperintense, relative to white matters on T1-weighted images and extensively enhanced by gadolinium on T2-weighted images [6]. The tumor radiographic findings are important consideration in the differential diagnosis. One of the main differential diagnoses of NENE is Jugulotympanic paraganglioma. Bierry et al. has presented several radiographic findings to distinguish between these two tumors. They found that although NENE and Jugulotympanic paraganglioma appear as tissue lesions with significant enhancement on CT and MRI, only paraganglioma has specific clinical features such as pulsatile tinnitus, a close relationship between tumor and Jacobson nerve or its branches, and vascular blush on angiography. In contrast, NENE are clearly separated from the Jacobson nerve and its branches, and even though they show highlighted contrast, they have expressionless angiographic [7].

Pathology

Macroscopically, tumor is typically soft, rubbery to firm, unencapsulated, white grey or red brown. Most tumors measure < 1 cm in size [15]. Histologically, they are infiltrative, showing moderately cellularity. A variety of growth patterns can be identified, including glandular/tubular, solid, sheet like, trabecular, cystic, nested, cribriform and single cell. The glandular structures occur individually or have back to back growth pattern. The intervening stroma is usually sparse and may be desmoplastic (Fig. 1). Granuloma may be seen. The neoplastic cells show a dual cell population with inner luminal eosinophilic cells, often associated with secretions, surrounded by abluminal basal cuboidal to columnar cells. The cells may have prominent plasmacytoid appearance especially in the solid areas. The nuclear chromatin ranges from hypochromatic to granular (Fig. 2). Cellular pleomorphism may be seen but mitoses are uncommon and necrosis is absent. Perineural invasion may rarely occur [15]. Histochemical stains show that the luminal and cytoplasmic secretions are positive for alcian blue and PAS [15]. By immunohistochemistry (IHC), tumor cells are variably but consistently positive for pan-cytokeratin, CAM5.2, EMA, chromogranin, synaptophysin, CD56, and various polypeptides (human pancreatic polypeptides) and

Fig. 1 Neuroendocrine neoplasm of the ear showing solid and nested pattern with glandular structures. The intervening stroma is scant and fibrotic (X200)

Fig. 2 Neuroendocrine neoplasm of the ear. The tumor cell exhibit bland cytology and hypochromatic to granular chromatin (X400)

transcription factors [13] (Fig. 3). Dual cell pattern has been reported with CK7 staining the luminal cells, as well as p63 and CK5/6 staining the abluminal cells (Fig. 4). Variable staining for S100 and CK20 is identified. SMA, Desmin, TTF1, CDX2, and PAX8 are negative [1].

Differential Diagnosis

The differential diagnosis of NENE is extensive and includes Jugulotympanic paraganglioma, acoustic neuroma, meningioma, endolymphatic sac papillary tumor, rhabdomyosarcoma, and adenocarcinoma [3]. However, the histologic, radiographic and immunohistochemical features of NENE

Fig. 3 Neuroendocrine neoplasm of the ear; chromogranin immunohistochemical stain (X100)

Fig. 4 CK7 immunohistochemical stain highlights the dual pattern in the tumor (X400)

help to distinguish them from other entities (Table 1) [3]. Jugulotympanic paraganglioma is the most common tumor of the middle ear. Similar to NENE, conductive hearing loss is the most common symptom of Jugulotympanic paraganglioma. Histologically, Jugulotympanic paraganglioma typically shows nested pattern (zellenballen) and a highly vascular stroma which differ it from NENE. Moreover, the glandular features and the keratin positivity seen typically in NENE are absent in Jugulotympanic paraganglioma. By IHC, S100 is negative in NENE but positive in Jugulotympanic paraganglioma in sustentacular pattern [6]. The histology of endolymphatic sac papillary tumor with the presence of papillary formations and its aggressive clinical course with bone invasion and intracranial extension differ markedly from those of NENE [3]. Meningioma shows

Table 1 Immunohistochemical stains in the differential diagnosis of NENE

	CK	EMA	S100	CG	SYN	NSE	DES	VIM	GFAP
NENE	Pos	Pos	V	Pos	Pos	Pos	Neg	Neg	neg
JTP	Neg	Neg	Pos*	Pos	Pos	Pos	Neg	Neg	Neg
MEN	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Pos	Neg
AN	Neg	Neg	Pos	Neg	Neg	Pos	Neg	Neg	Neg
RMS	V**	V**	Neg	V**	V**	V**	Pos	Pos	Neg
ESPT	V	V	V			V	Neg	V	V

NENE neuroendocrine tumors of the ear, *JTP* jugulotympanic paraganglioma, *MEN* meningioma, *AN*: acoustic neuroma, *RMS* rhabdomyosarcoma, *ESPT* endolymphatic sac papillary tumor, *CK* cytokeratin, *EMA* epithelial membrane antigen, *CG* chromogranin, *SYN* synaptophysin, *NSE* neuron specific enolase, *DES* desmin, *GFAP*: glial fibrillary acidic protein, *VIM* vimentin, *Pos* positive, *Neg* negative, *V* variable, *in the sustentacular cells, **typically negative but can have aberrant expression in 30–50% if the alveolar subtype

whorled meningotheial pattern with intranuclear inclusions and frequent psammoma bodies. These features are absent in NENE. Additionally, meningioma lacks the expression of the neuroendocrine markers seen in NENE [15]. Compared to the primary and metastatic adenocarcinomas of the ear, NENE lack the aggressive histologic features (pleomorphism, necrosis, and increased mitoses) and invasion of bone and adjacent structures that are usually seen in these tumors [10]. Rhabdomyosarcoma (including alveolar rhabdomyosarcoma) seldom occurs the ear [6]; alveolar rhabdomyosarcoma can rarely show an aberrant epithelial and neuroendocrine expression by IHC. However, the morphologic features of RMS along with the positive staining for the muscle markers distinguish this tumor from NENE [2]. Unlike NENE, acoustic neuroma is typically well circumscribed, showing histology that resembles schwannoma with fascicles, alternating hypocellular and hypercellular patterns, and Verocay bodies, and is diffusely positive for S100 [3]. In addition, glandular metaplasia may occur in the setting of chronic otitis media and mimic NENE but the glandular proliferations in chronic otitis media are typically focal, haphazardly arranged, and associated with fibrosis, chronic inflammation, and calcifications [3].

Treatment and Prognosis

Complete surgical resection is the primary treatment of NENE, including removal of the ossicles [4]. The tumor typically peels away easily but recurrence might occur if the middle ear bones are not included in the resection. Surgery can be conservative if the tumor is small and confined to the middle ear or more radical including mastoidectomy if the tumor is large or extensively involves the adjacent structures [15]. Tumor may involve the parotid gland by direct extension and this does not constitute metastatic disease [15]. Recurrence or persistent disease occurs in 15% of cases [15]. Metastasis may occur and death has been reported; however,

due to difficult assessment of the literature with the disputable tumor classification and the limited number of reported cases, further investigations are required to ascertain tumor biology [15].

Conclusion

NENE are rare causes of middle ear mass. The etiology of these tumors is not clear and their classification is not well defined. However, it is important to accurately recognize these tumors in order to perform the prompt correct management and limit the tumor morbidity. Furthermore, these tumors may recur and metastasize despite the consideration of being low aggressive tumors; therefore, further studies with long term follow up are needed to ascertain their biologic behavior.

Acknowledgements The author thanks Dr. Bin Xu for providing samples for images.

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