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Original Article

Neuroendocrine neoplasms of the middle ear: report of 2 cases and review of the literature

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Abstract: Neuroendocrine adenoma of the middle ear is a rare tumor of the middle ear. The origins, as well as classification of the disease, are still controversial. We reported 2 cases of neuroendocrine adenoma of the middle ear separately in a 60-year-old male and a 48-year-old patient who both presented with hearing loss. This article reviewed the reported literatures and summarized the pathogenesis, clinical features, imaging manifestations, pathological features, and biological behavior of neuroendocrine adenoma of the middle ear, so as to improve the understanding of the disease.

Keywords: Neuroendocrine neoplasms of the middle ear, hearing loss, surgical treatment, adenoid structure

Introduction

Neuroendocrine adenomas of the middle ear are rare tumors, accounting for less than 2% of all middle ear tumors [1]. At present, the classification, etiology, and biological characteristics of these diseases are not clear. The existing research tends to believe that it is a kind of low-grade malignant lesion with mild cell morphology and local recurrence, but there is still a great controversy about the existence of distant metastasis [2]. To better characterize this rare entity, we reviewed our case archive with respect to clinical characteristics, pathological features, and immunohistochemistry.

Case report

Case 1

A 60-year-old male patient was admitted to the hospital for left ear fullness, tinnitus and conductive hearing loss. A physical examination showed a mass at the left lateral auditory meatus and the tympanic membrane was not visible. Further computed tomography (CT) scan depicted a mass with soft tissue density without evidence of bone invasion (**Figure 1A**). The medical record revealed the surgical history of tympanitis in the right ear. Finally, the patient received excisional biopsy and transcanaltympanoplasty. Intraoperatively, the tumor invades the tympanic chamber of the left ear and perforation in the posterior upper quadrant of the tympanic membrane could be seen. The tumor was completely removed and sent to the pathology department for further histopathological examination.

The gross examination was described as followed: the tumor was gray red and firm measured 1.5×1×0.5 centimeter in size. Under low magnification, the tumor presented a growth mode in which the adenoid structure coexisted with trabecular (**Figure 1B**). In the glandular growth mode, the lesion showed a typical dual cell population with an inner, flattened cell surrounded by abluminal basal cuboidal to columnar cells. Eosinophilic amorphous secretions could be found in the glandular cavity (**Figure 2A**). Mitoses are rarely to be seen and necrosis is absent. Consisting of columnar cells with round nuclei, the trabecular structure also showed moderate cellularity. The chromatin

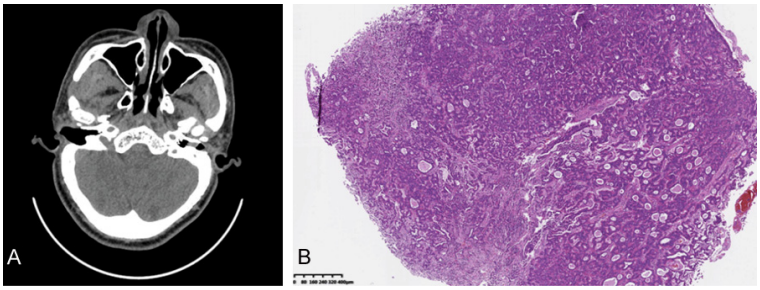

Figure 1. A. CT scan depicted a mass with soft tissue density without evidenceof bone invasion. B. At low magnification, the tumor showed coexistence of various growth patterns (H&E 40×).

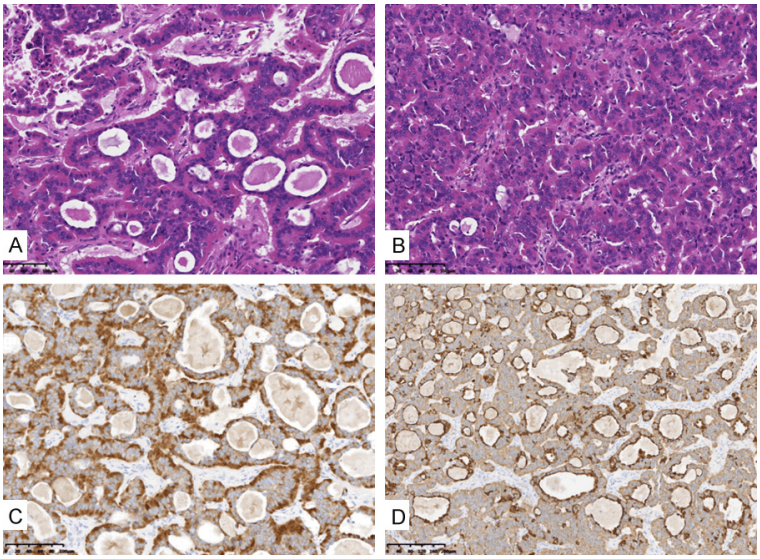

Figure 2. A. Histologic examination showed a typical dual cell population in the glandular growth mode with eosinophilic amorphous secretions in the glandular cavity (H&E 200×). B. The trabecular structure was mainly composed of columnar cells with round nuclei with moderate cellularity (H&E 200×). C. Diffuse cytoplasm stain for Syn of abluminal cells (200×). D. Positive stain for CK of inner cells (100×).

tended to present a homogenous to finely granular morphology (**Figure 2B**).

By immunohistochemistry, the bilayered luminal-abluminal arrangement was confirmed with CK staining the inner cells, as well as Syn staining the abluminal cells (**Figure 2C**, **2D**). Ki67 varied from 1 to 2%, and CD56 is negative in tumor cells.

Case 2

The 48-year-old male patient was admitted because of recurrent purulence in the right ear and hearing loss for more than 10 years. The symptoms could be alleviated after antibiotic treatment. Now, the patient presented with hearing loss in the right ear accompanied by tinnitus. A physical examination revealed mucopurulent secretions in the right lateral auditory canal and there was a perforation on the right tympanic membrane with proliferated granulation tissue around it. CT scans showed a relative lower soft tissue density in the right middle ear canal and no obvious destruction was observed in ossicular bones. Then the patient underwent right transcanal tympanoplasty. After a complete removal of the tumor, the specimen was sent to the pathology department for examination.

Macroscopically, the tumor is rubbery, unencapsulated, white grey and red brown. Measured 0.9×0.5×0.3 cm in size, the irregular mass had a rough surface. Histologically, the lesion predominantly showed trabecular growth pattern composed of cuboidal-to-columnar cells with minimal pleomorphism (**Figure 3A**, **3B**). The cytoplasm was eosinophilic and tended to present a “salt-and-pepper” pattern. The tumor was of moderate cellularity without mitoses and necrosis. In this case, the sparse intervening stroma can be observed. Immunohistochemistry showed consistent expression of CgA and Syn (**Figure 3C**), while no CD56 expression was seen. Also, the proliferation index was low (less than 1%) (**Figure 3D**).

Discussion

At present, the etiology and classification of neuroendocrine tumors in the middle ear are still controversial. Bell et al. suggested that tumors may originate from undifferentiated progenitor cells [2]. It has been suggested that tumors are associated with undifferentiated pluripotent stem cells derived from neural crest [2-4]. Pelosi et al. asserted that tumors may

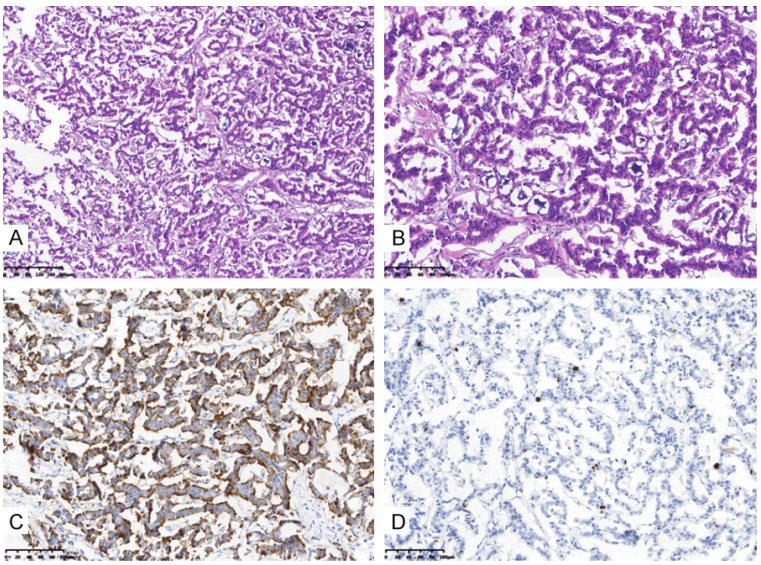

Figure 3. A. Histologically, the tumor presented trabecular growth pattern composed of cuboidal-to-columnar cells with the sparse intervening stroma (H&E 100×). B. The cell morphology is mild with minimal pleomorphism (H&E 200×). C. Positive stain for Syn of tumor cells (200×). D. Ki-67 proliferation index was low in tumor cells. (200×).

originate from translocation or residual embryonic residues of glandular cells in the middle ear mucosa [1]. Hyams and Michaels first proposed the concept of middle ear adenoma in 1976 and described it. Among the 20 cases of middle ear tumors reported, their morphology was not consistent with paraganglioma or known salivary gland tumors, so they named it as middle ear adenoma [5]. In 1980, Murphy et al. reported a similar middle ear tumor, which was labeled carcinoid because of its ultrastructural and histochemical features. Since then, similar cases have been reported, but these tumors have been labeled with various names, including middle ear adenomas, carcinoids, adenomatous tumors, adenocarcinoids, and amphoteric adenomas [5-7]. Currently, there is a tendency to classify these tumors according to their immunohistochemical markers and metastasis [7]. Saliba et al. have proposed to classify middle ear gland tumors into three types, namely Saliba classification: type I is middle ear neuroendocrine adenoma, accounting for 76% of tumors, positive immunohistochemistry, without metastasis; type II is middle ear adenoma, accounting for 20%, immunohistochemical expression is negative, no metastasis; type III tumor only accounts for 4%, is a middle ear carcinoid, with positive immunohistochemical expression and metastatic or even has carcinoid syndrome [8].

The average age of tumorigenesis was about 50 years old (14-80 years old) [4]. No significant gender difference was found. The most common and main symptoms were progressive hearing loss [7]. Other common manifestations were blockage or stress, tinnitus, vertigo, etc [8]. Facial paralysis can also occur in a few patients [9]. It is believed that facial paralysis is related to anatomical abnormalities or local compression of tumors rather than invasion of tumors. After surgical resection, the clinical symptoms can usually be alleviated or even completely disappeared [3]. Otolaroscopy often shows the complete tympanic membrane. Usually tumors are confined to the middle ear but it can also extend to the tympanic chamber [1]. In a few cases, tumors can penetrate the tympanic membrane and extend into the external auditory canal or mastoid bone [2, 9]. At present, only one case has been reported to have paraneoplastic syndrome [6].

On the CT, the tumor is characterized by soft tissue density in the mastoid bone without blood vessels, which can be extended to the middle ear and mastoid. The bone expansion is common in the middle ear space, which is related to bone remodeling and bone shell [1]. The ossicular chain is usually embedded into the tumor, but there is no bone erosion [4].

Grossly, the cut surface is white gray or reddish brown; most tumors are less than 1 cm in diameter. Under low magnification, with back-to-back glandular pattern, adenoid structure predominates in diversed growth pattern [2, 4], and the cavity often contains amorphous mucin secretion. The lesions generally present as bilayer cells with eosinophilic cytoplasm in the inner cavity and columnar cubic cells in the surrounding basement. This pattern can be better confirmed by electron microscopy and immunohistochemical staining [3]. Other common growth patterns of tumors include solid, lamellar, trabecular, cystic, nested and sieve-shaped, pseudohemangioma-like, plasma cell-like, etc [9]. It has been reported in literature that typi-

cal plasma cell-like appearance is often seen in the solid structure area [1]. Microscopically, cell pleomorphism is often seen, but mitotic phenomena rarely occur. Generally, there is no necrosis [2]. Sometimes tumor cells may present as Paget-like pattern [3, 9].

Tumors generally express broad-spectrum cytokeratin and neuroendocrine markers, including CK7, CgA, NSE, and Syn [1, 2]. CK7 is strongly and uniformly expressed in endoluminal cells of adenoid structure, and also expressed in other growth structures to varying degrees. Neuroendocrine markers are positive in basal cell layer of adenoid structure, which to some extent proves the double-layer cell morphology of adenoid structure. HPP was focally positive in the lesions [3]. It has been reported that CAM5.2, EMA, CD56, S-100, LEU-7, serotonin, glucagon, adrenocorticotropic hormone, somatostatin, various polypeptides as well as transcription factors can also be expressed in different degrees in cancer cells [1, 3]. Abbas et al. showed that ISL1 was strongly and diffusely expressed in the nuclei of all neuroendocrine tumors of the middle ear [9].

Middle ear neuroendocrine adenomas need to be differentially diagnosed with a range of diseases, including cervical tympanic ganglionoma, adenoid cystic carcinoma, endolymphatic papillary tumor, meningioma with glandular structure, acoustic neuroma, rhabdomyosarcoma as well as other primary and metastatic adenocarcinoma of the ear. Similar to neuroendocrine adenomas of the middle ear, cervical tympanic paraganglioma may also present with progressive hearing loss, but the latter is also characterized by pulsatile tinnitus. Morphologically, typical paragangliomas are often presented as “zellballen” pattern, with vascular-rich stroma, which can help to differentiate it from neuroendocrine adenomas of the middle ear. Immunohistochemistry, negative expression of S-100, and strong positive expression of Keratin strongly support the diagnosis of neuroendocrine tumors in middle ear [4]. Acinar rhabdomyosarcoma shows a pattern of alveolar growth, but rarely occurs in the middle ear. Immunohistochemical staining of smooth muscle markers is positive and does not express epithelial and neuroendocrine markers, which can help identify neuroendocrine adenomas [10]. At the same time, it has been reported that galanin is negative in carcinoid tumors, while positively expressed in some paragangliomas [11]. Molecular pathological examination of squamous rhabdomyosarcoma may have chromosomal translocation t (2; 13) (q35; q14) [12]. The endolymphatic papillary tumor presents a destructive invasive growth, often accompanied by bone invasion or intracranial extension. This invasive biological behavior is significantly different from that of the middle ear neuroendocrine adenoma [1, 11]. Acoustic neurinoma’s histological morphology is similar to that of schwannomas in which cell-rich areas and cell-depleted areas alternate. Verocay corpuscle-like structures can be found. Immunohistochemically, S-100 showed diffuse positive. Microscopically, meningiomas with adenoid structures may exhibit characteristic spiral and gravel structures, while immunohistochemical staining lacks neuroendocrine markers [13]. Compared with middle ear neuroendocrine adenomas, other primary and metastatic adenocarcinomas in the middle ear often show significant cellular pleomorphism, increased necrosis and mitotic figures, and even involvement of bone and adjacent tissues, which neuroendocrine adenomas often lack these invasive histological features [14].

It is noteworthy that Tomazic et al. reported a case of neuroendocrine adenoma of the middle ear in which the clinical manifestation presented as chronic otitis media accompanied by facial nerve paralysis. Therefore, the author suggested that the diagnosis of neuroendocrine adenoma of the middle ear should be considered in the differential diagnosis of chronic otitis media when conservative treatment was ineffective and facial nerve paralysis occurred [15]. Complete surgical excision, including the removal of ossicles, is the main treatment for neuroendocrine adenomas of the middle ear [15]. When the ossicular chain is encapsulated by tumors, patients with ossicular chain resection have better prognosis, while those without ossicular chain resection have a recurrence rate of 18-22% [4]. Although there is not enough evidence to suggest that one operation is superior to another, the recurrence rate of tympanoplasty (14%) is higher than that of radical mastoidectomy (9%). Adjuvant therapy with radiotherapy, chemotherapy, or somatostatin analogues is not recommended [4, 8]. Recurrence is reported in about 15-20% of cases [3, 16]. Tumors extend directly to the parotid gland, but do not constitute metastatic diseases [9].

Literatures have reported metastasis and death: Mooney et al. first reported a patient with metastases [16]. In the existing literature, two patients developed cervical lymph node metastasis 3.5 and 7 years after initial diagnosis and operation respectively [3, 16]. Another case report described a case of metatarsal metastases in a middle ear carcinoid tumor 10 years after resection [17]. In a cohort of studies conducted by Diana et al., one patient had cervical lymph node involvement and two patients had distant metastases involving the liver and bones respectively [2].

Therefore, the authors believe that although the neuroendocrine adenomas of the middle ear are low-grade malignant, long-term follow-up is necessary to clarify its biological behavior.

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Disclosure of conflict of interest

None.

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