Adenoma of the middle ear is a primary tumor of the middle ear that can have exocrine (mucinous) and/or neuroendocrine differentiation. It is an uncommon tumor in the practice of otolaryngology. Based on the first description by Hyams and Michael in 1976, adenoma of the middle ear is defined as a benign adenomatous tumor arising from the middle ear mucosa. To date, there have been over 100 cases reported in English literature, but none by Chinese authors. However, two cases of "carcinoid tumor of the middle ear" have been reported in Chinese literature [1, 2]. These middle ear tumors with predominantly neuroendocrine differentiation are now known to be adenomas. For its rarity, debates still exist regarding its histogenesis, grading and nomenclature. In this paper, we review the literature on middle ear adenoma with an eye toward improving its diagnosis and management.

Anatomical background

The middle ear, bounded by the tympanic membrane and inner ear, contains the malleus, incus and stapes, the opening of the eustachian tube, the attic (epitympanic recess) and the mastoid cavity.

There is a progressive transition in the histological appearance of the middle ear mucosa from the Eustachian tube to the mastoid. Pseudostratified and cylindrical epithelium covers the anterior third of the tympanic cavity, whereas epithelium in the middle portion of the cavity can have up to three layers of cells. The posterior third of the tympanic cavity, the antrum of the mastoid, and the ossicles are covered by single layer of cells. The majority of middle ear epithelial cells are not ciliated, except for those of the anterior third around the opening of the Eustachian tube. Tubuloalveolar seromucosal glands are found in the lamina propria of the pharyngeal part of the Eustachian tube, whereas the tympanic cavity, the antrum, and the mastoid do not have such components [3]. Two types of secretory cells can be identified in normal mucosa of the middle ear: goblet and intermediate cells.

Embryologically, the middle ear epithelium is an endodermal (foregut) derivative, while mesenchymal elements of the middle ear (including the ossicles) are derived from mesodermal elements of the branchial arch [4].

Histogenesis and nomenclature

Early authors described adenoma of the middle ear as a benign adenomatous tumor arising from the mucosal epithelium. Later, others found that some glandular tumors of the middle ear, otherwise apparently identical to an adenoma, showed neuroendocrine features (i.e., positive Grimelius staining, abundance of membrane-bound granules on electron microscopy and expression of neuroendocrine immunohistochemical markers). These are termed "carcinoid tumor of the middle ear".

Typical carcinoid tumor, by definition, is a low-grade malignant neoplasm. They are more commonly diagnosed in the lung, pancreas and gastrointestinal tract. It is well-known that carcinoid tumor originate from neuroendocrine cells that are dispersed throughout these tissues. Neuroendocrine cells are derived from pluripotential endodermal stem cells and can secrete hormones. However, neuroendocrine cells have not been identified either in normal or inflamed middle ear mucosa, although an undifferentiated, pluripotential endodermal stem cell may still be present within the surface mucosa of the middle ear.
However, some authors have found immunohistochemical and ultrastructural evidence that both adenoma and carcinoid tumor of the middle ear show features of exocrine(mucinous) and neuroendocrine differentiation, although the proportion of the two types of differentiation is different [8-9]. Therefore, debates remain regarding whether carcinoid tumors of the middle ear represent an entity distinct from middle ear adenoma. The confusion results from histopathologic similarities between tumors classified under both terms, inaccurate and inconsistent terminology for middle ear tumors, uncertainty regarding histogenesis, and similarities in biological behavior.

Multiple recent studies have demonstrated that these terms describe the same tumor, which can have mixed patterns of differentiation [8-11]. Tumors with either exocrine(mucinous) or neuroendocrine differentiation most likely represent opposite ends of the spectrum of differentiation. Based on a histopathologic and immunohistochemical study of 48 cases, Torske et al [11] suggested using "neuroendocrine adenoma of the middle ear" as a more descriptive term, for it not only reflects its dual nature but also its benign clinical behavior. Moreover, they propose an undifferentiated, pluripotential endodermal stem cell to be the origin of the tumor.

In the World Heath Organization (WHO) Classification of Tumors (2005), adenoma of the middle ear is defined as a benign glandular neoplasm showing variable differentiation along neuroendocrine and mucin-secreting pathways. Middle ear adenomatous tumor, neuroendocrine adenoma of the middle ear and carcinoid tumor of the middle ear are considered the synonyms of adenoma of the middle ear in the WHO classification [12]. This proposal is gradually accepted by Otolaryngologists and Pathologists.

**Pathologic findings**

Intraoperative examination of middle ear adenomas often shows solid neoplasms, apparently encapsulated and not particularly vascular, usually white, gray, or reddish brown in color. They can be easily peeled off the bony walls of the middle ear but may entrap and destroy the ossicles. Torske et al [11] reported tumor sizes ranging from 0.2 to 3.0 cm, with an average of 0.8 cm. Ramsey et al [13] reported ossicular involvement in 72% (33/46) of their cases, with 20% mastoid involvement and 9% eustachian tube involvement rates.

On routine light microscopy, the histological architectural patterns of middle ear adenomas can be solid, glandular, or trabecular. Over 81% of cases present with more than one pattern [11]. Tumor cells are usually uniform and can be cuboidal or cylindrical. They have a moderate amount of acidophilic cytoplasm and may assume a plasmacytoid appearance [14]. Nuclei are round to oval with a "salt and pepper" chromatin pattern and inconspicuous nucleoli. Moderate to marked nuclear pleomorphism can occur, but neither mitotic activity nor necrosis are features of middle ear adenoma [15]. The tumors can produce mucin, which is positive on periodic acid-Schiff, alcian blue, and mucicarmine stains. Papillary features are not present in a middle ear adenoma. However, sheet-like and disorganized areas can be identified in some cases of middle ear adenoma which may be artificial and related to surgical tugging on the specimen at resection.

In a study involving 48 cases, middle ear adenomas were positive for cytokeratin(CK) cocktails (90%), CAM 5.2 (81%), and CK7 (90%). Staining with CK7 highlighted the luminal surface of glandular cells. Only focally and weakly positive results were observed with CK20(6%). Neuroendocrine markers such as chromogranin(88%), neuron-specific enolase(50%), synaptophysin(31%), and serotonin(25%) were positive, but not all markers were positive in a single case. Neuroendocrine markers were positive within the basal cell layer of the glandular elements. They were more diffusely positive in other architectural patterns. Reactivity, however, was not uniform and varied both between cases and in levels of intensity. Human pancreatic polypeptide was focally positive in most cases(94%), and S-100 protein was positive in some stromal cells (18%) or tumor cells (15%) [11].

We recently treated a case of middle ear adenoma in a 27-year-old man presenting with aural fullness, tinnitus of one year and hearing loss of one month. The tumor was gray-white, soft and about 0.5×0.5 cm in size. Histological sections of the tumor showed regular, columnar or cuboidal eosinophilic cells arranged in solid, trabecular and glandular areas(Fig 1 and 2). Mild nuclear pleomorphism was present, and mitotic figures were absent. The tumor was immunohistochemically positive for CK8/18 and synaptophysin and negative for S-100 protein and P63 (Fig 3 and 4).
Ultrastructural examination of five cases showed basally situated cells and solid tumour cells (cell B) containing neuroendocrine granules which were positive for neuroendocrine makers. This was in contrast to apically situated dark cells (cell A) which contained mucous granules, reacted with antikeratin and antiepithelial membrane antigen antibodies but stained negative for neuroendocrine makers \[3, 12\]. Both cells A and B were small, rounded, regular and hyperchromatic, without mitosis or atypical core.

The value of frozen section is controversial, as some middle ear adenomas have been mistaken for adenocarcinomas on frozen section. In a series of 32 frozen sections of middle ear adenomas, the final diagnosis of middle ear adenoma was not made in any case by frozen section. Some of the diagnoses were paraganglioma (21 cases), chronic otitis media (6 cases), and cholesteatoma (5 cases) \[16\]. However, Jones et al reported a case diagnosed on frozen section biopsies, which helped avoiding unnecessary procedures \[17\].

No molecular genetic studies have been conducted on middle ear adenomas. The tumor is not reported to occur in families \[12\].

**Clinical features**

Adenoma of the middle ear is an uncommon neoplasm and constitutes about 4% of aural tumors \[11\]. Patient age ranges from 14 to 80 years, with no sex predominance. The mean age is about 45 years. All patients present with unilateral disease, with no side predominance. The most common symptom is hearing loss, followed by a mass and aurial pain \[4, 11, 13, 15\]. Retrospectively reviewing 48 cases of middle ear adenoma, Torske et al found that 69% of the patients presented with hearing loss, followed by a mass (25%), aurial pain (24%), discharge (14%), tinnitus (12%) and facial nerve weakness (8%) \[11\]. These were similar with Ramsey’s report \[13\]. The duration of symptoms ranged from 1 to 228 months, with an average of 21 months. Some patients presented with no symptoms and the tumors were detected at the time of routine physical examination.

Otoscopy often shows an intact tympanic membrane in the first stage with a dark brown reddish colored structure behind it. Sometimes this mass distorts the tympanic membrane, bending in the direction of the external auditory canal. Tumor may later expand and penetrate the tympanic membrane. For some patients, an external auditory canal mass can be the only finding at the time of diagnosis. A middle ear mass can develop later.

Audiometry examination identifies a conductive hearing loss in the majority of patients with middle ear
adenoma, and sensorineural hearing loss (SNHL) in some patients. The conductive loss of approximately 30 dB prevails in the conversational frequencies.

Computed tomography (CT) of the temporal bone is a key procedure. It highlights a nonspecific soft-tissue density, well limited mass in the tympanic cavity without bone invasion and poses mainly the differential diagnosis from a glomic tumor. Sometimes ossicular entrapment and destruction can be observed. On magnetic resonance imaging (MRI), these tumors often have brain-like signal intensity on both T1- and T2-weighted images, with no significant enhancement after intravenous gadolinium.

For our patient, pure tone audiometry showed a mix hearing loss of 48 dB HL in the right ear with a 15 dB air-bone gap. Hearing was normal in his left ear. Temporal bone CT revealed a soft tissue density mass within the right tympanic cavity entrapping the ossicles (Fig 5).

**Diagnosis and differential diagnosis**

For its nonspecific findings in the clinic and on imaging studies, the diagnosis of adenoma of the middle ear depends mainly on post-operative pathologic examination. Indolent course, CT examination, typical features of histopathology and findings of immunohistochemical examinaton compose of the main factors in the diagnosis of adenoma of the middle ear.

The differential diagnosis of benign tumors of the middle ear includes middle ear adenoma, paragangioma and schwannoma. A paragangioma is composed of uniform epithelioid cells, which are grouped in ball-like cell clusters orzellballen. These clusters are surrounded by spindle-shaped sustentacular cells. The epithelial cells are immunohistochemically positive for neuroendocrine markers, such as synaptophysin and chromogranin A.

The epitheloid cells are immunohistochemically negative for cytokeratin markers. The sustentacular cells are immunohistochemically positive for S100 protein. A schwannoma is a benign nerve sheath tumor composed of Schwann cells. These form hypercellular areas (Antoni A areas) and hypocellular areas (Antoni B areas). They may contain Verocay bodies, which are composed of 2 parallel columns of palisading cells. Schwannomas are diffusely immunohistochemically positive for S100 protein.

The differential diagnosis of middle ear lesions also includes other benign lesions such as cholesteatoma and chronic otitis media. A cholesteatoma is composed of anucleate keratin-filled squamous cells with foreign body giant cells and hemosiderin. Cholesteatoma can be diagnosis according to its distinct macroscopy and histopathology. Chronic otitis media can have glandular metaplasia as well as chronic inflammation and granulation tissue.

Malignant tumors of the middle ear, such as adenocarcinoma, must be distinguished from middle ear adenoma. Adenocarcinomas of the middle ear are often metastasis from other sites. Based on its benign biologic behavior, mature tumor cell differentiation and CT findings, middle ear adenoma can be distinguished from adenocarcinoma.

**Management**

Surgical excision constitutes the only curative treatment of the lesion. No additional therapy is recommended in the literature. Surgical excision also allows histological analysis of the lesion and exploration of the entire tympanic cavity and the mastoid. Excision must be complete and constitutes the only possibility of no recurrence.

The pre-operative evaluation mainly consists of otoscopy, CT of the temporal bone and audiometry examination. The surgical procedure mainly consists of radical mastoidectomy or tympanotomy. In a retrospective review of 46 cases, 48% of the patients underwent radical mastoidectomy whereas 34% patients underwent tympanotomy. A 29% of recurrence rate was related to tympanotomy versus 10% to radical mastoidectomy.

If the tumor entraps the ossicles, the ossicles are often recommended to be partly removed to ensure complete excision of the tumor. As the ear with middle ear adenoma often has normal Eustachian tube function and middle ear mucosa, ossiculoplasty should have a successful outcome.

**Prognosis**

Middle ear adenomas have a good prognosis after surgical excision and most tumors do not recur. Recurrence has occurred after incomplete surgical resection. No patient deaths were reported in a series of 48 cases. Eight of these cases were recurrent, but they were successfully treated with surgical resection.

Some authors have reported that facial nerve
involvement is a poor prognostic indicator. However, others have indicated that facial nerve involvement is most likely related to nerve compression and not invasion. Facial nerve symptoms may resolve after resection [21]. Unlike carcinoid tumors of the lung, which have a metastatic rate of less than 23%, only 4 cases of middle ear adenoma metastasis have been reported [13]. One of these cases was cervical lymph node metastasis, and the other three cases were intraparotid lymph nodes. No case with distal metastasis has been reported.

References


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