

The Auricular Carbuncle-Middle Ear Adenoma

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Preface

Neuroendocrine adenoma of the middle ear was initially described by Hyams and Michaels in 1976 [1]. Neuroendocrine adenoma is an exceptional, non secretory, benign, glandular neoplasm demonstrating minimal tumour aggression with gradual, localized progression. The adenomatous tumour depicts neuroendocrine and epithelial differentiation, may delineate a continuum with carcinoid tumour and can be contemplated as an adenocarcinoid neoplasm. Contemporary World Health Organization (WHO) classification designates the neoplasm as an adenoma with neuroendocrine features. Tumour reoccurrence with localized and distant metastases may ensue, possibly indicative of a low-grade malignancy.

The neoplasm is additionally designated as ceruminoma, ceruminous adenoma, adenomatous tumour, carcinoid, adenocarcinoid or an amphicrine tumour. Appropriate clinical and morphological discernment of the haemorrhagic, vascular neoplasm is challenging and frequently delayed. Thus, cogent tissue sampling with pertinent immunohistochemistry is necessitated.

Disease characteristics

Neuroendocrine adenoma of middle ear comprises of below < 2% of primary neoplasms of the ear. Middle ear segments in their entirety can be implicated. Nevertheless, chronic otitis media and cholesteatoma are unrelated conditions [2,3].

A gender-specific predilection is absent. Tumefaction is generally discerned within second decade to fifth decade and no age of tumour emergence is exempt [2,3].

Infrequently, the neuroendocrine neoplasm exhibits localized tumour invasion, localized tumour reoccurrence and a potential for distant metastasis [2,3].

Tumefaction may impede the middle ear, encompass middle ear ossicles and extend into the mastoid. Occasionally, the neoplasm perforates tympanic membrane and extends into external auditory canal. Localized tumour reoccurrence may appear following a median duration of 6 years [2,3].

Glandular neoplasia of the middle ear are classified into distinct subtypes contingent to expression of neuroendocrine immune markers and occurrence of distant metastases:

- Type I is a commonly discerned (76%) variant of neuroendocrine adenoma of the middle ear. Characteristically, the neoplasm is immune reactive to various neuroendocrine markers. Distant tumour metastasis is absent [2,3].

- Type II variant (20%) is a middle ear adenoma which manifests immune non reactivity to diverse neuroendocrine markers. Distant tumour metastasis is absent [2,3].
- Type III variant (4%) is designated as carcinoid tumour of the middle ear, appears as an infrequent neoplasm and is typically immune reactive to various neuroendocrine markers. Distant tumour metastasis is usually exhibited [2,3].

Aforesaid subtypes of middle ear glandular adenoma may represent as a singular entity with diverging neuroendocrine differentiation, possible emergence of distant metastases and are associated with a favourable prognosis. Type I variant and type II variant may depict localized tumour reoccurrence although are devoid of distant metastases. Type I variant delineates tumour reoccurrence or persistent disease in around 15% instances. Extended tumour monitoring is mandated [2,3].

The tumefaction commonly arises from the middle ear epithelium and exemplifies epithelial and neuroendocrine differentiation. Tumefaction may be engendered from mucosal cells of the middle ear. Besides, tumour may originate from distant, embryonic nests of glandular cells situated within the middle ear mucosa [2,3].

Alternatively, tumefaction is posited to arise from undifferentiated, pluripotent, endodermal stem cells as epithelial cells with neuroendocrine differentiation are absent in the middle ear [2,3].

Clinical elucidation

Essentially, clinical representation and features of middle ear adenoma are non-specific. Individuals can manifest aural fullness, recurrent otalgia, itching, headache, tinnitus, mucopurulent otitis, facial nerve paralysis, otorrhoea and postural instability [4,5].

Neurological symptoms may or may not be present. Headache may emerge as cluster headaches, typically exhibiting severe pain within the frontal and temporal regions [4,5].

Predominant clinical symptom is conductive deafness wherein proportion of hearing loss is contingent to magnitude and location of the neoplasm [4,5].

Generally, incriminated individuals demonstrate deafness, otalgia and fullness of the ear. Occasionally, the neuroendocrine neoplasm may be associated with carcinoid syndrome with emergence of diarrhoea, abdominal cramps, cutaneous flushing and bronchoconstriction. Tympanic membrane is usually intact [4,5].

Histological elucidation

Upon gross examination, a grey/white to reddish-brown, firm, rubbery, well circumscribed, un-encapsulated tumefaction with a mean magnitude of 0.8 centimetres is encountered. Tumour associated haemorrhage is absent although tumour parenchyma may be haemorrhagic. Middle ear ossicles can be intact and encompassed by the neoplastic tissue. Erosion of inner ear and facial canal is absent [4,5].

Upon microscopy, variable neoplastic configurations such as cellular sheets, solid areas, trabeculae, cystic articulations, cribriform pattern or glandular structures are delineated. Generally, papillary architecture is absent [4,5].

Tumour glands or tubules are layered with uniform, singular layer of cuboidal or columnar epithelial cells incorporated with variable quantities of eosinophilic cytoplasm and spherical to elliptical, hyperchromatic nuclei with eccentric nucleoli. Neoplastic cells may appear plasmacytoid and demonstrate significant cellular and nuclear pleomorphism. The circumscribing stroma is sparse, fibrotic or myxoid. Mitotic activity is minimal to absent. Necrosis is absent [4,5].

Tumefaction is composed of uniform cells of moderate dimension which lack cellular diversity. The loosely cohesive cells configure a diffuse pattern of growth and a plasma-like appearance [4,5].

Tumour cells may articulate mucin which is reactive to periodic acid Schiff's (PAS) stain. Tumefaction can depict neuroendocrine differentiation upon morphology and immunohistochemistry [4,5].

Upon ultrastructural examination, tumour cells depict desmosomes, microvilli and foci of glandular differentiation. Membrane bound dense core granules are commonly discerned [5,6].

Upon immunohistochemistry, neoplastic cells are reactive to neuroendocrine markers such as synaptophysin, chromogranin or neuron specific enolase (NSE) and epithelial markers as keratin, cytokeratin 7, cytokeratin 20, cytokeratin AE1/AE3 or Cam 5.2 along with mucin, lysozyme, serotonin and S100 protein [5,6].

Tumour cells are immune nonreactive to p63, CD56 and actin. Proliferation marker Ki-67 is minimally reactive and appears at below < 3% [5,6].

Differential diagnosis

Neuroendocrine adenoma of the middle ear requires segregation from neoplasms such as:

- Acoustic neuroma which is composed of foci of glandular metaplasia wherein glands may be haphazardly disseminated within zones of chronic otitis media. The neoplasm is configured of spindle-shaped cells with elongated nuclei and fibrillary cytoplasm. Specific zones of tumour configuration are described as Antoni A areas and Antoni B areas. Antoni A area is miniature and predominantly composed of organized, interwoven, elongated, bipolar cells. Antoni B area is represented by random accumulation of cells circumscribing foci of cystic change, necrosis, ancient haemorrhage and vascular articulations. Lymphocytic infiltrate is variable and nuclear pleomorphism can be observed. Focal necrosis and mitotic figures are exceptional. Oedema, micro-cysts, macro-cysts, xanthomatous alterations and focal calcification are associated with degeneration of tumour tissue [6,7].
- Jugulotympanic paraganglioma demonstrates a classic, organoid pattern with the configuration of a "zellballen" or nesting of tumour cells. Tumefaction is constituted of centric, spherical or elliptical chief cells imbued with abundant, eosinophilic, granular or vacuolated cytoplasm and uniform nuclei with dispersed chromatin. Spindle-shaped, basophilic, peripheral sustentacular cells circumscribe tumour cell nests and are immune reactive to S100 protein. Tumour cells may depict cellular and nuclear pleomorphism. Tumour cell aggregates are segregated by a prominent fibro-vascular stroma. Occasionally, dense fibrous stroma may encircle clusters of tumour cells. An infiltrative pattern of tumour evolution is encountered. Mitotic figures or foci of necrosis are exceptional. Glandular or alveolar differentiation is absent [6,7].
- Meningioma is composed of spherical, elliptical or spindle-shaped tumour cells configuring whorls, nests or a lobular pattern. Tumour cells are imbued with pale cytoplasm, punched out nuclei with intra-nuclear cytoplasmic inclusions and demonstrate indistinct cell borders. Psammoma bodies may be discerned along with microscopic foci of bone invasion. Cholesteatoma frequently accompanies the neoplasm. Tumour cells are immune reactive to epithelial membrane antigen (EMA) and vimentin [6,7].
- Middle ear adenocarcinoma is constituted of tumour cells displaying significant cellular and nuclear pleomorphism, nuclear anaplasia, mitotic activity, foci of tumour necrosis and infiltration of adjoining bone or soft tissue. Tumefaction depicts an absence of dual cell layering of neoplastic glands and singular, luminal epithelial cells may coat the glands. Well differentiated

neoplasms may simulate a middle ear adenoma with invasive tumour configuration. The neoplasm can represent as an adenoid cystic carcinoma or muco-epidermoid carcinoma [6,7].

Additionally, conditions such as vascular malformations, cholesteatoma, chronic otitis media, schwannoma, endolymphatic sac papillary tumour, rhabdomyosarcoma, teratoid tumour and squamous cell carcinoma require a distinction [6,7].

Pertinent histology, imaging and immunohistochemistry is recommended for an accurate tumour discernment and segregation [6,7].

Investigative assay

Upon physical examination, tympanic membrane may be intact although whitish material can exude at retro-tympanic area. Otoscopy demonstrates a bulging, reddish tumefaction superimposed by an intact tympanic membrane. Audiometric analysis may be normal or displays moderate, conductive deafness [8,9].

Computerized tomography (CT) of brain can depict inflammation of hypo-tympanum and meso-tympanum of the incriminated ear. CT scan displays a soft tissue mass of variable magnitude confined to the middle ear which can obstruct the orifice of eustachian tube [8,9].

Magnetic resonance imaging (MRI) demonstrates a mass of variable magnitude confined to the middle ear or a tumefaction expanding into the eustachian tube. Magnetic resonance imaging (MRI) may depict isointense lesions upon diffusion-weighted imaging [8,9].

The neoplasm may abut bone petal of internal carotid artery although erosion of circumscribing bone is absent. Tumefaction depicts an intense enhancement following administration of gadolinium contrast. MRI can be performed in order to monitor localized or residual disease [8,9].

CT and MRI usually exhibit non specific features although the imaging modalities can be gainfully employed for evaluating extent of disease and erosion of middle ear ossicles [8,9].

Osteolytic destruction of middle ear ossicles is exceptional and emerges as a feature which demarcates the neoplasm from cholesteatoma and middle ear adenocarcinoma [8,9].

Positron emission computerized tomography (PET-CT) demonstrates an absence of localized or distant tumour metastases [8,9].

An excisional biopsy may be adopted for appropriate tissue sampling and discernment of the neoplasm [8,9].

Therapeutic options

Comprehensive surgical extermination of the uncommon neoplasm is an optimal therapeutic strategy. Complete surgical resection is the primary, preferred methodology for treating neuroendocrine adenoma of the middle ear [8,9].

Extent of comprehensive or radical surgical excision is contingent to tumour magnitude and associated bony erosion of middle ear ossicles. However, preservation of the ossicles enhances possible tumour reoccurrence [8,9].

Radical surgical resection can be adopted to eradicate residual disease with procedures such as tympanoplasty with eradication of stapes, footplate and preservation of optic capsule. Posterior tympanotomy may be employed in order to approach the tumefaction confined to and adherent with mesotympanum or hypotympanum and encompassing middle ear ossicles in the absence of bony erosion. Mastoidectomy may be required in order to excise enlarged lesions. Inadequate surgical eradication is associated with tumour reoccurrence [8,9].

Adjuvant radiotherapy may be beneficially employed. Localized tumour reoccurrence and distant metastasis can be optimally managed with radiotherapy. Besides, radiotherapy may induce malignant metamorphoses of the neoplasm. Antibiotic therapy may be instituted although is superfluous [8,9].

However, chemotherapy is not contemplated as a viable treatment option [8,9].

Postoperative audiometric examination is necessitated which may demonstrate superior auditory residue. Preoperative conductive deafness may ameliorate postoperatively. The neoplasm is associated with a favourable prognosis [8,9].

Tumour monitoring can be performed and tumour reoccurrence or persistence can be evaluated with frequent otoscopy and an annual MRI. Bone-anchored hearing aids may be adopted in order to ameliorate loss of hearing [8,9].

With an indolent biological course, an uncertain malignant potential, ability for localized tumour reoccurrence, regional and distant metastases and infrequent tumour-associated morbidity an extensive surgical demolition of the neoplasm with tumour-free surgical margins is recommended. Long-term clinical and investigative follow-up is necessitated in order to monitor tumour progression [8,9].



Figure 1: Middle ear adenoma demonstrating a reddish brown neoplasm behind an intact tympanic membrane [10].

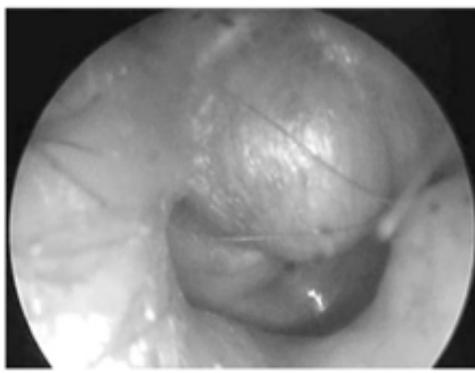


Figure 2: Middle ear adenoma exhibiting a bulbous neoplasm adjacent to an intact tympanic membrane [11].

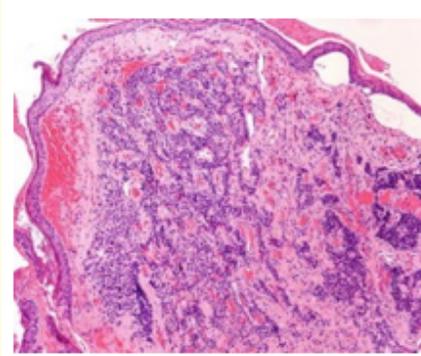


Figure 3: Middle ear adenoma delineating a neuroendocrine pattern with glands layered by uniform cells with singular nucleus and abundant, eosinophilic cytoplasm [12].



Figure 4: Middle ear adenoma enunciating a neuroendocrine tumour configuring a glandular pattern with uniform cuboidal cells, singular nucleus, abundant cytoplasm and eccentric nucleolus [13].

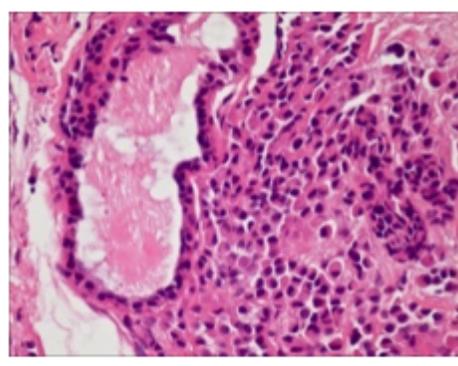


Figure 5: Middle ear adenoma exemplifying an organoid tumour pattern with layering columnar epithelial cells imbued with eosinophilic cytoplasm, regular nuclei and an intervening fibro-vascular stroma [14].

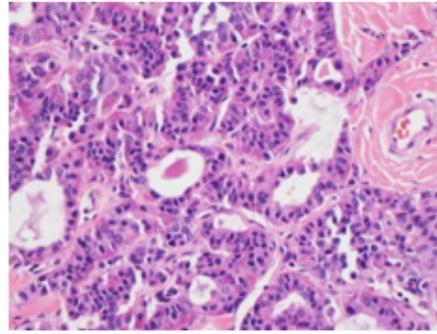


Figure 6: Middle ear adenoma demonstrating an organoid tumour pattern with regular cuboidal cells, abundant eosinophilic cytoplasm, uniform nuclei and circumscribing fibro-vascular stroma [15].

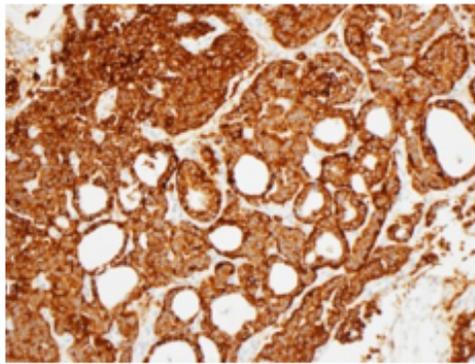


Figure 7: Middle ear adenoma exhibiting tumour cells immune reactive to synaptophysin [15].

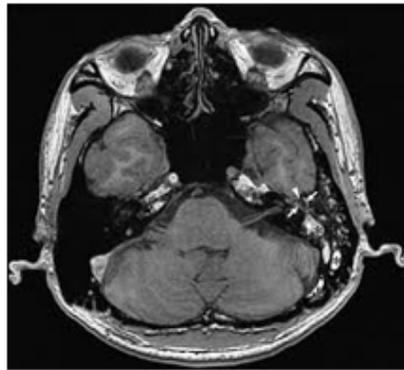


Figure 8: Middle ear adenoma enunciating discontinuity of middle ear ossicles with bony erosion [16].

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