Ceruminous Neoplasms of the Ear

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Abstract

Ceruminous glands are modified apocrine glands located in the external auditory canal (EAC). Neoplastic lesions arising from these glands are rare in humans and constitute a major differential diagnosis for glandular neoplasms of the EAC. Due to anatomic restrictions, benign and malignant neoplasms present with similar symptoms and to some extent even comparable radiologic features, particularly when the tumors are localized. Biopsies are frequently limited by small size, fragmentation and improper anatomic and architectural orientation, thereby hampering our ability to appreciate the relationship of peripheral edges of the tumor to the surrounding tissue. Benign and malignant tumors may also have overlapping histomorphologic features, which further magnifies the challenges in accurate diagnosis and management strategies. This article summarizes the salient clinical, radiologic and histologic features of common ceruminous gland tumors, in addition to discussing features that can aid in differentiating ceruminous tumors from other EAC tumors and to distinguish benign from malignant entities.

Keywords Ceruminous · Adenoma · Carcinoma

Ceruminous glands are modified apocrine glands located primarily in the skin lining cartilaginous/membranous portion of the external auditory canal (EAC) [1]. The medial bony part of EAC and the auricle are normally devoid of these glands, although they can be seen rarely as an incidental finding. There are typically 1000–2000 ceruminous glands with no obvious morphologic or numerical difference between both men and women. However, African Americans tend to have higher number, density and function of these glands, compared to Caucasians. Though the number of glands does not increase with age, the full secretory capacity is reached only after puberty and decreases with age.

Normal Morphology

Ceruminous glands are coiled tubular glands similar to eccrine glands of the skin, the ducts of which empty their contents into a hair follicular infundibulum or directly onto the skin surface. Histologically, they are characterized by

rounded clusters of variably dilated tubules (Fig. 1), lined by two concentric layers of epithelium. The inner/luminal layer is prominent, characterized by large cuboidal to columnar cells with abundant eosinophilic cytoplasm and homogenous ovoid nuclei that are located at the basal aspect of the cells. Some cells may display brownish-yellow lipofuscin/ceroid pigment along the luminal aspect of the cells, which is positive for periodic acid-schiff, sudan black and acid-fast stains [2]. In actively secreting glands, the luminal cells are more columnar with deeply eosinophilic cytoplasm, apical blebs or rounded protrusions and the lumina frequently contain proteinaceous material; whereas inactive glands have dilated empty lumina lined by flattened epithelial cells. The outer layer of epithelium has myoepithelial differentiation; is typically flattened and may be difficult to appreciate in cross sections [3]. Each tubular structure is limited by a basement membrane.

Immunohistochemical and Histochemical Markers

Both the luminal and basal cells stain positive with keratin cocktails and epithelial membrane antigen [2]. Luminal cells are typically positive for CD117, MUC1, cytokeratin (CK) 7 and 19, while the myoepithelial cells express S100, p63,

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Fig. 1 Ceruminous glands: normal morphology. **a** Skin lining external auricular canal reveals rounded clusters of variably dilated glands located in mid to deep dermis, flanked by pilosebaceous units superficially and cartilage in the deep aspect (H & E, magnification: $\times 20$). **b** The glands are composed of columnar cells with abundant eosinophilic cytoplasm in the luminal aspect, while the outer (myoepithe-

lial) layer may be variably attenuated (downward arrow); granular eosinophilic secretion may be present in the lumen. Some of the luminal cells have brown cytoplasmic pigment (upward arrow) and apical blebs, characteristic of apocrine secretion (H & E, magnification: $\times 600$)

smooth muscle actin, CK5/6 and glial fibrillary acidic protein, in addition to being positive for high molecular weight CK cocktails [2, 4]. Mucicarmine special stain may be helpful in highlighting the presence of intracytoplasmic mucin [5].

Function and Biologic Significance

The apical blebs of the luminal epithelial cells are pinched off into the lumina (decapitation secretion) as part of secretions, which then combine with sebum to produce cerumen. The ceruminous glands express several antimicrobial proteins including IgA, β -defensins, lysozyme, MUC1, lactoferrin, and cathelicidin, which appear to concentrate in the luminal aspect of the cells and apical blebs; thus, becoming part of the secretions and contribute to local immunity [4, 6]. The secretory function of ceruminous glands is slow and continuous, but may increase in response to adrenaline, although they lack direct innervation [7]. The pH of the EAC is maintained by the secretions around 5.7 in the inner/medial aspects of

canal, while it becomes more alkaline towards the meatus [8]. The secretory capacity progressively decreases with increasing age, coinciding with increased risk for external ear infections in the elderly.

Ceruminous Gland Neoplasms and Nomenclature

Ceruminous gland neoplasms are extremely uncommon in humans, though they are relatively common in other mammals [9, 10]. Glandular tumors of the EAC constitute only 2.4% of all ear neoplasms [11]. Originally, these tumors have been called by several names, including ‘ceruminoma’ for both benign and malignant entities [2, 12]. Refinement of nomenclature of ceruminous neoplasms to reflect the histologic features and biologic behavior was initiated by Pulec [13] and Wetli et al. [14]. Currently, World Health Organization (WHO) recognizes 2 categories of ceruminous neoplasms: malignant and benign [15, 16] (Table 1).

Table 1 Ceruminous gland neoplasms

Benign/ceruminous adenomas	Ceruminous adenoma Ceruminous pleomorphic adenoma Ceruminous syringocystadenoma papilliferum
Malignant/ceruminous adenocarcinomas	Ceruminous adenocarcinoma Ceruminous adenoid cystic carcinoma Ceruminous mucoepidermoid carcinoma

Evaluation of Patients

Most patients present with complaints of a mass and/or other non-specific symptoms that are related to the size of the mass, rate of growth, degree of ear canal obstruction and infiltration into adjacent organs, including nerves [8, 17]. Duration of symptoms ranges from a few months to years. In most slow-growing tumors including majority of the benign lesions, mass, fullness, hearing loss and pruritus are the most common symptoms. Pain and otorrhea may be secondary to superimposed infection. Low-grade carcinomas such as adenoid cystic carcinoma also present with similar symptoms, but pain develops in majority of the patients fairly early in the course. Rapidly growing tumors are typically characterized by pain, bleeding, otorrhea, mass and secondary otitis externa. Tinnitus, nerve palsies and asymptomatic presentation are uncommon. Patients may also present with symptoms consistent with chronic otitis media.

However, there is significant overlap between the presentation and clinical features of benign and malignant tumors. Therefore, a thorough evaluation including review of patient's medical history (to exclude other head and neck tumors); comprehensive physical examination (to evaluate for neural changes or paralysis, extension or metastasis from other head and neck tumors, particularly of parotid); full otoscopic evaluation (to determine the size of tumor and degree of EAC obstruction, to evaluate for secondary cholesteatoma and tympanic membrane integrity); CT-scan and MRI (to determine the extent of tumor, involvement of middle ear and infiltration of underlying bone and adjacent organs and to exclude other head and neck tumors); culture of any discharge (to identify and treat potential infections); and in select cases, auditory evaluation (to determine the type of hearing loss and extent of middle and inner ear involvement) is essential.

Significance of Optimal Biopsy and Thorough Histologic Evaluation

Since EAC tumors often tend to be small and localized, early diagnosis is extremely challenging. Due to the complex anatomy of this region, not only is it often difficult to assess the extent of tumors clinically, but obtaining adequate biopsy is also problematic, leading to superficial, fragmented or partial biopsies in many cases. However, such biopsies are inadequate for definite diagnosis, since there is significant overlap in histologic features of benign and malignant entities and may lead to misleading diagnosis [18]. An excisional biopsy and/or wide local

excision of the tumor with a rim of uninvolved tissue is recommended. The advantages of obtaining adequate biopsies is two-fold: (i) ability to completely evaluate the growth pattern of the tumor and its relationship to the surrounding tissue, (ii) avoiding biopsy-related distortion of residual tumor and stroma, and thus, preventing over-call of pseudoinfiltrative tumor nests as carcinoma. In addition, since there is considerable overlap in clinical presentation, a thorough histopathologic evaluation of the tumor is essential for diagnosis [19]. Certain clinical and histologic features may aid in differentiating these tumors (Table 2); some of these features may be highly specific, but are not common or easily identified and hence, they are not very sensitive. Therefore, a comprehensive histologic analysis of adequate biopsies as well as integration of the clinical presentation and radiologic features is necessary to arrive at the correct diagnosis.

Benign Ceruminous Neoplasms

Also referred to as 'ceruminous adenomas', they comprise benign glandular proliferations of ceruminous origin and account for 5.7% of all EAC and auricular tumors [17, 20] (Table 1). The most common entities include ceruminous gland adenoma, ceruminous pleomorphic adenoma and ceruminous syringocystadenoma papilliferum. Other extremely uncommon tumors include apocrine hidradenoma [21, 22] and cylindroma [19, 23]. However, the latter two entities have not been recognized in the 4th edition of WHO classification of head and neck tumors [15, 20]. In a retrospective study of 41 cases, definite sex predilection was not observed; however, the mean age at presentation was higher among women compared to men (56.6 vs. 52.1 years) and the average duration of symptoms was longer in women compared to men (23.3 vs. 13.3 months) [17], similar to previously reported [20]. However, the tumor size on average was smaller in women compared to men (1.0 vs. 1.2 cm). The lesions are typically well-circumscribed without destruction of surrounding structures (Table 2). Imaging studies (CT-scan and MRI) typically reveal a well-defined space occupying soft tissue lesion with homogeneous or rarely non-homogeneous enhancement with or without cystic changes within the EAC [24]. The mass may be associated with widening of the canal, but, bone infiltration is not identified [25]. Features of otitis media and mastoid cavity changes suggestive of cholesteatoma may also be present [26].

Ceruminous Gland Adenoma

Ceruminous gland adenomas (CGA) are the most common benign glandular neoplasms of the EAC [17]. Mass in the outer half of EAC and hearing difficulties are the most

Table 2 Features that may aid in distinguishing benign and malignant ceruminous neoplasms

Features	Benign	Malignant
Presenting symptoms		
Duration of symptoms	Longer	Shorter
Mean age at diagnosis	~ 6th decade	~ 5th decade
Nerve paralysis ^a	None	Common
Radiologic features		
Destruction of ear canal	None	Common
Infiltration into surrounding structures ^a	None	Common
Histologic features		
Tumor silhouette ^a	Well-circumscribed	Poorly circumscribed
Infiltrative growth ^a	None	Present
Growth patterns ^a	Tubular, cystic, papillary > solid	Solid, cribriform > tubular, papillary, cystic
Cellularity	Low to moderate	Moderate to high
Perineural invasion ^a	None	Common
Lymphovascular invasion ^a	None	Common
Necrosis ^a	None	Common
Stromal changes	Sclerosis	Desmoplasia
Mitotic rate	Low (0.3/10 HPF)	High (3/10 HPF)
Atypical mitotic figures ^a	None	Common
Cytologic atypia	Mild to moderate	Moderate to marked
Myoepithelial cell number and distribution ^a	Numerous, subjacent to luminal apocrine cells	None or few in in-situ component, if any
Lipofuscin (ceroid) pigment	Present	None
Prominent nucleoli ^a	Rare	Common
Clinical course		
Recurrence ^a	Uncommon	Common, multiple
Metastasis ^a	None	Common

^aHighly specific features, but not sensitive

common presenting symptoms, followed by discharge, pain and neural symptoms. The average duration of symptoms was 17.0 months. The tumors may also be essentially asymptomatic and identified incidentally in some patients. CGA are diagnosed typically in adults, on average in the 6th decade of life. However, rare cases of pediatric CGA have been described, arising de novo [27, 28] or in association with nevus sebaceous [29]. Associated cholesteatoma may be present.

Grossly, the lesions are grey to pink polypoid masses with smooth or rarely verrucoid surface and firm consistency. They are non-encapsulated, but well-circumscribed tumors with occasional surface involvement. The lesion is composed of glandular structures lined by two-layers of epithelium typically arranged in lobulated clusters (Fig. 2). Focal papillary structures, solid and cystic pattern of growth may be present. The luminal cells display abundant eosinophilic cytoplasm with scattered yellowish-brown cytoplasmic pigment, while the myoepithelial cells may be variably prominent. The stroma may be hyalinized in some areas, and glands located in these areas may display a pseudoinfiltrative

pattern of growth. Necrosis, frank cellular pleomorphism, atypical mitotic figures, thickening or cylindrical deposition of basement membrane material, perineural and lymphovascular invasion is not identified.

Ceruminous Pleomorphic Adenoma

Ceruminous pleomorphic adenoma (CPA), also referred to as mixed tumor is the second most common benign glandular neoplasm of the EAC [17]. Progressively enlarging mass and pain are the most common presenting symptoms [21, 25]. There is a slight male predominance (8:5) and the mean age at presentation is 50.5 years, while the duration symptoms is shorter compared to CGA [17]. Also, the tumors on average tend to be larger than CGA. The histogenesis of these tumors has been a subject of debate; some authors have speculated these tumors to arise from ectopic salivary glandular tissue, although such glands have not been documented [30]. Local extension from parotid may occur [31] and therefore, should be excluded by critical evaluation of

Fig. 2 Ceruminous adenoma. **a** The lesion is composed of lobulated proliferation of glandular structures with open lumina (H & E, magnification: $\times 100$). **b** The luminal cells display abundant eosinophilic cytoplasm with scattered yellowish-brown cytoplasmic pigment (arrow), while the outer myoepithelial layer may be variably attenuated (H & E, magnification: $\times 600$)

patient's prior history, thorough physical examination and imaging studies.

The tumors are typically non-encapsulated and well-circumscribed with firm grey-white cut surface. Histologically, there is haphazard proliferation of tubulo-glandular structures lined by two-layers of epithelium [17] (Fig. 3). Apocrine differentiation and cytoplasmic brownish pigment may be present, focally. The cells lack pleomorphism, necrosis and prominent mitotic activity. The background stroma is hypocellular, composed of myxochondroid or even mucoid matrix. Rarely, adipocytes may constitute the predominant mesenchymal component [32] and such lipomatous variants are extremely rare even among pleomorphic adenomas of the major salivary glands [33].

Ceruminous Syringocystadenoma Papilliferum

Syringocystadenoma papilliferum (SCAP) is an extremely rare tumor of EAC and only a handful of cases have been reported so far [17, 24, 34–37]. The presenting symptoms include mass, discharge, pain, hearing loss, otorrhea and tinnitus; duration of symptoms ranged from 3 months to 10 years. The lesions were polypoid tumors or subcutaneous lesions, some which may be ulcerated. Majority of the lesions were diagnosed in the 7th to 8th decades of life.

Grossly the tumor may be polypoid, lobulated or ulcerated. Histologically, they are characterized by multiple short, thick papillae lined by two-layered epithelium projecting into cystic spaces (Fig. 4). Plasmacytic infiltrate is usually identified in the fibrovascular cores, but can be sparse and patchy. In two cases, circumscribed proliferation of double-layered glandular structures, consistent with tubular apocrine adenoma was present subjacent to the papillary proliferation

Fig. 3 Pleomorphic adenoma. **a** The lesion is composed of haphazard proliferation of compressed tubulo-glandular structures in a background of hypocellular chondromyxoid stroma (H & E, magnification: $\times 100$). **b** The cells have moderate amounts of eosinophilic

cytoplasm, suggestive of apocrine differentiation, but lack pleomorphism, necrosis and prominent mitotic activity (H & E, magnification: $\times 400$)

Fig. 4 Syringocystadenoma papilliferum. The lesion is composed of multiple short, thick papillae lined by two-layers of cuboidal to columnar epithelium projecting into cystic spaces. The fibrovascular cores typically contain plasmacytic infiltrate (H & E, magnification: $\times 100$)

[35, 36], of which one had lipomatous stroma [36]. Attention to the background skin is essential to exclude an associated nevus sebaceous [38, 39], since both SCAP and tubular apocrine adenoma may be associated with nevus sebaceous.

Malignant Ceruminous Neoplasms

Malignant ceruminous neoplasms, also referred to as ‘ceruminous adenocarcinomas’ in the WHO classification of head and neck tumors (Table 1) [16, 20] appear to be slightly more common than their benign counterparts. However, whether this is due to reporting bias is unclear [20]. They include adenoid cystic carcinoma; adenocarcinoma, not otherwise specified and mucoepidermoid carcinoma in the descending order of frequency [2]. Other extremely uncommon malignancies of ceruminous glands include mucinous carcinoma [40]. There is a slight predilection for women (male to female ratio- 4:5). The average age at presentation for carcinomas is about a decade earlier compared to ceruminous adenomas. In addition, age greater than 60 years at diagnosis may be associated with decreased survival [41]. The tumors most commonly arose from the posterosuperior quadrant of the lateral EAC [2]. Tumor size ranged in size from 0.5 to 3.0 cm, with a mean diameter of 1.55 mm, with women typically having smaller tumors compared to men (average 1.4 vs. 2.0 cm). Wide infiltration into the surrounding tissue with destruction of osseous and cartilaginous structures and invasion along nerves is common (Table 2). Imaging studies (CT scan and MRI) reveal heterogeneously enhancing tumor infiltrating and effacing the surrounding tissues, with obliteration of EAC [18]. Extension into infratemporal fossa and invasion of surrounding soft tissues and parotid gland may be present [42].

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ADCC) is the most common type of glandular malignancy arising from the ceruminous gland [2]. ADCC are at least twice as common as the other types of ceruminous carcinomas [2]. There is no sex predilection. Pain, mass, hearing changes and otorrhea are the most common presenting symptoms followed by recurrent/chronic otitis externa, bleeding and neural symptoms, including facial nerve paralysis [11]. The average duration of symptoms is approximately 9.3 months, and the mean tumor size is 1.6 cm [2].

The tumors are unencapsulated and poorly circumscribed with diffuse infiltration into the surrounding tissue (Fig. 5). The tumor is composed of monomorphic basaloid cells with small amounts of clear cytoplasm and hyperchromatic ovoid nuclei. The cells are arranged in irregularly shaped tubular or cribriform nests of varying size surrounding basement-like material entrapped within pseudoglandular spaces. In some cases, this material can also be seen around the tumor nests, and can occasionally be abundant. Myxoid/mucinous change is common and range from focal to extensive. Tumor cells can also proliferate as expansile nests (solid pattern), the presence of which is associated with worse prognosis [11, 43, 44]. Tumor necrosis and overt cellular pleomorphism are rare. Perineural invasion is common and can be multifocal. Genetic alterations of MYB family of transcription factors, including translocations have emerged as the primary oncogenic drivers in ADCC of other organs [45, 46]. It is unclear if similar alterations are also present in ADCC derived from ceruminous glands.

Several histopathologic features correlate with increased risk for recurrence and hence, a poor prognosis, including (i) solid pattern of growth, (ii) bone invasion, (iii) perineural invasion and (iv) positive resection margins [11, 37]. Secondary involvement of surrounding tissues including parotid gland, also portends a poor outcome. In addition, prolonged duration of symptoms (more than 2 years) is associated with recurrence [47].

Ceruminous Adenocarcinoma

Ceruminous adenocarcinoma (not otherwise specified) is the 2nd most common type of carcinoma arising from ceruminous glands [2] and predominantly affect adult women and men. The most frequent presenting symptoms include mass, hearing changes, otorrhea/bleeding, pain and paralysis of 6th, 7th, 12th or other cranial nerves [2, 8, 37, 42], followed by lymphadenopathy and tinnitus. The

Fig. 5 Adenoid cystic carcinoma. **a** The tumor is widely infiltrative, composed of small to medium sized nests of variable shapes and sizes (H & E, magnification: $\times 20$). **b** The tumor is composed of monomorphic basaloid cells with small amounts of cytoplasm and hyperchromatic ovoid nuclei, arranged in irregularly shaped tubular or cribriform nests of varying sizes, surrounding basement material entrapped within the pseudoglandular spaces (H & E, magnification: $\times 200$). **c** Perineural and intraneural invasion are common (H & E, magnification: $\times 200$)

lesions measure 1.7 cm (mean) in size and the average duration of symptoms is 5.8 months [2].

Ceruminous adenocarcinoma is characterized by irregularly shaped and sized clusters, nests and solid sheets of atypical epithelial cells widely infiltrating the surrounding tissue (Fig. 6). The epithelial cells have large hyperchromatic nuclei or vesicular chromatin with prominent nucleoli

and with at least focal glandular differentiation. Tumor necrosis (geographic or comedo pattern) as well as papillary structures can be identified. The surrounding stroma is often desmoplastic with variable inflammatory infiltrate. Perineural and lymphovascular invasion may be present. Two populations of tumor cells or in-situ component may be focally evident in some cases, supporting ceruminous

Fig. 6 Ceruminous adenocarcinoma, not otherwise specified. **a** The tumor is characterized by irregularly shaped and sized nests and solid sheets of atypical epithelial cells with focal glandular differentiation, infiltrating the surrounding tissue (H & E, magnification: $\times 40$). **b** Tumor necrosis (top right) and lymphovascular invasion (arrow) (H & E, magnification: $\times 200$). **c** Perineural invasion (H & E, magnification: $\times 400$) may be present

origin. Ceruminous adenocarcinoma can also be classified as high-grade and low-grade tumors based on the extent of glandular differentiation and the proportion of solid areas [37, 42]. Rarely, the tumor can be well-differentiated, presenting as mucinous carcinoma [40]. Pagetoid involvement of the overlying epidermis is rare [48]. To date, no specific histologic feature has been definitely shown to correlate with patient outcome. Recurrence, regional and systemic metastases occur frequently despite adequate surgical resection with negative margins [49].

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the least common type of ceruminous gland adenocarcinoma and only a handful of cases have been reported in the literature [2, 13, 20, 50–54]. The most common presenting symptoms include mass, pain, tinnitus, and dizziness. Compared to other ceruminous malignant tumors, the duration of symptoms is longer for MEC (mean 24 months) and the tumors tend to be larger in size (mean 3.0 cm) [2].

Histologically, the tumors are composed of a variable mixture of squamoid/epidermoid (epithelioid cells with dense eosinophilic cytoplasm, patchy keratinization and intercellular bridges), mucin-producing glandular (epithelioid cells with small nucleus that is compressed by intracytoplasmic vacuole and highlighted by mucin stains such as mucicarmine) and intermediate (ovoid cells with hyperchromatic nuclei and pale pink cytoplasm, with capacity for epidermoid or glandular differentiation) cells (Fig. 7) [55]. The tumors are graded histologically into three categories: low, intermediate and high grades on the basis of growth pattern: pushing versus infiltrative; presence of lymphovascular invasion, perineural infiltration, coagulative tumor necrosis, prominent cellular pleomorphism; mitotic rate and

percentage of cystic component [56, 57]. Due to the rarity of the tumor, it is unclear if this grading system is applicable to MEC of ceruminous origin. Also, these neoplasms have not been evaluated for t(11; 19), a (q12; p13) translocation resulting in MECT1 and the MAML2 gene fusion, noted frequently in MEC of other organs [58]. The outcome in patients with ceruminous MEC may depend on the histologic grade of the tumor [2, 53, 54].

Differential Diagnoses

Due to rarity of ceruminous neoplasms, they are frequently a diagnosis of exclusion. Benign and malignant neoplasms that arise from ceruminous glands have overlapping clinical features and morphologic characteristics. Therefore, other tumors of epidermal, EAC, middle ear and mastoid origin such as hidradenoma [21, 22], cylindroma [19, 23], cholesteatoma, choristoma, exostosis, osteoma, eosinophilic granuloma, paraganglioma [59, 60], branchial cleft cysts, basal cell carcinoma [61, 62], squamous cell carcinoma [63, 64], melanoma [65, 66], neuroendocrine adenoma of the middle ear [67–69], meningioma [70, 71], and extension of benign or malignant salivary gland tumors from parotid gland [31] constitute the major differential diagnoses [28]. Thorough histologic evaluation and imaging studies are essential for accurate diagnosis. Table 3 summarizes the clinical and histologic features and relevant immunohistochemical studies of the common differential diagnoses.

Outcome and Management

Complete surgical excision with negative margins is the mainstay in the management of EAC tumors. For benign neoplasms, wide local excision to remove all tumor with

Fig. 7 Mucoepidermoid carcinoma. **a** The tumor is composed of three populations of cells squamoid cells with dense eosinophilic cytoplasm, mucin-producing glandular cells and ovoid intermediate cells with hyperchromatic nuclei (H & E, magnification: $\times 400$).

b Mucicarmine special stain reveals the presence of glandular cells by highlighting the intracellular mucin vacuoles (mucicarmine stain, magnification: $\times 400$)

Table 3 Common differential diagnoses of benign and malignant ceruminous gland tumors

Tumor	Presenting symptoms and clinical features	Radiologic features	Histologic features	Positive immunohistochemical stains
Epidermal adnexal origin				
Eccrine cylindroma [19, 23]	Painless plaque or nodule	Non-erosive homogeneously enhancing lesion limited to EAC	Circumscribed tumor composed of solid nests of luminal and myoepithelial cells and hyaline material surrounded by a hyaline sheath	Luminal cells: CEA, CK7, CK19, EMA Myoepithelial cells: S100, p63, SMA, CK5/6
Epidermal origin				
Basal cell carcinoma [61, 62]	Bloody discharge, pain; nodular mass	Heterogeneous mass obliterating EAC, with variable bone erosion, and extension to middle ear and mastoid cavity	Nests and infiltrative cords of basaloid cells with minimal clear cytoplasm, with peritumoral clefting and variably myxoid stroma	p63, p40, CK5/6, Ber-EP4, CD10 (periphery of tumor nests)
Squamous cell carcinoma [63, 64]	Pain, discharge, bleeding, tinnitus, hearing loss, pruritus; exophytic ulcerated tumor	Heterogeneous mass obliterating EAC, with variable bone erosion, and extension to middle ear and mastoid cavity	Nested and infiltrative proliferation of epithelioid cells with variable amounts of eosinophilic cytoplasm, and ovoid nuclei; keratin pearls	p63, p40, CK5/6, EMA
Melanoma [65, 66]	Hearing loss, mass, bloody discharge; variably pigmented polypoid ulcerated mass	Soft tissue lesion with variable bone erosion	Nests of variably pigmented epithelioid, spindled or small cells, often associated with in situ component in the overlying epidermis	S100, SOX10, MART1/MelanA, HMB45, MITF, tyrosinase
Middle ear origin				
Neuroendocrine adenoma [67–69]	Fullness, tinnitus, hearing loss, pain, vertigo; retrotymppanic non-pulsatile mass	Soft tissue mass without bone erosion	Cribriform, trabecular, nested, lobular or solid proliferation of small to medium-sized epithelioid cells with finely speckled chromatin surrounded by fibrotic stroma	CK7, CK5/6, p63, synaptophysin, chromograninA, CD56
Others				
Meningioma [70, 71]	Hearing loss; subcutaneous mass	Soft tissue mass surrounded by thinning of cortical bone and adjacent reactive hyperostosis	Lobulated proliferation of epithelioid syncytial cells with scattered whorls and psammoma bodies	EMA, progesterone receptor
Paraganglioma [59, 60]	Hearing loss, occasional bleeding; firm subcutaneous mass	Soft tissue mass lacking bone erosion	Organoid or nested growth of epithelioid (chief) cells with eosinophilic cytoplasm, ovoid nuclei and speckled chromatin and inconspicuous spindled (sustentacular) cells	Chief cells: synaptophysin, chromogranin A, S100, cytokeratin Sustentacular cells: S100, GFAP

negative margins is essential to prevent recurrence [8]. Transmeatal excision is usually sufficient for small tumors, while retroauricular approach may be needed for larger tumors [25]. For patients with concomitant chronic otitis media, mastoidectomy and middle ear treatment may be necessary. The prognosis is overall favorable with only rare tumor recurrence. Radiation and other adjuvant therapies do not offer added benefit for patients with benign ceruminous neoplasms.

Carcinomas of ceruminous origin frequently recur locally, and may give rise to regional lymph node and systemic metastasis [2, 8]. Of the three types, ADCC has the most favorable outcome, with a mean survival of 8.3–10 years, compared to 1.5–4.7 years in other carcinoma types. The disease specific mortality is 30.4% for ADCC, 35.0% for ceruminous adenocarcinoma and 22% for MEC (all grades) [2, 8, 37, 50–54]. ADCC is prone to recurrence even after adequate treatment and may recur in more than 40% of patients and the recurrences can be multiple [18, 47]. The rate of distant metastasis is reported to be around 27% [47]; lungs are the most common sites, followed by brain and bone [47, 72]. Ceruminous adenocarcinoma are also prone to recurrence and metastasis [49]. Ceruminous MEC have been historically reported to have a poor prognosis [2]; however, recent reports suggest that patients with low-grade MEC may have a relatively good outcome [53, 54].

Due to the proximity to middle ear, mastoid and temporal bone, infiltration into the surrounding organs including bone and the possibility of extension through fissures such as fallopian canal, foramen of Huschke, petrotympanic fissure and fissures of Santorini, wide en bloc resection to include the osseous portion of EAC with partial tympanomastoidectomy is recommended for surgical resection of carcinomas [2, 8, 53]. Large tumors or recurrence may necessitate extended radical mastoidectomy and total parotidectomy. Intracranial extension may require excision of the involved portion of dura. Adjuvant radiation therapy is indicated for large tumors, high-grade carcinomas and for recurrent tumors [2, 8, 53]. Analysis of SEER database revealed that patients that underwent radiation therapy had decreased survival compared to those that did not [41]. This is likely a reflection of the advanced tumor stage and aggressive nature of these carcinomas. Chemotherapy is not a common modality of therapy [8, 50]. Continued follow-up is necessary to identify local, regional and distant recurrence and to implement appropriate therapy.

Summary

Ceruminous neoplasms are uncommon tumors of the EAC that present with protean clinical presentation in addition to having considerable morphologic overlap between benign

and malignant neoplasms. Therefore, comprehensive evaluation including physical examination, multimodal imaging studies and thorough histologic evaluation of an adequate biopsy that includes surrounding tissue is necessary to arrive at the correct diagnosis. Complete surgical excision with negative margins is the preferred treatment for benign and malignant tumors; adjuvant and palliative measures include radiation therapy and rarely chemotherapy.

Compliance with Ethical Standards

Conflict of interest The author declares no funding or conflicts of interest to disclose.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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