Ceruminous Adenomas

A Clinicopathologic Study of 41 Cases With a Review of the Literature

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Background: Ceruminous gland neoplasms are rare neoplasms. To date, a large clinicopathologic study of benign ceruminous gland neoplasms has not been reported.

Design: Forty-one cases of ceruminous gland adenomas diagnosed between 1970 and 2000 were retrieved from the files of the Armed Forces Institute of Pathology. Histologic features were reviewed, immunohistochemical analysis was performed (n = 21), and patient follow-up was obtained (n = 40).

Results: The patients included 22 men and 19 women, 24 to 85 years of age (mean, 54.2 years). Patients presented clinically with a painless mass of the outer half of the external auditory canal (n = 33) or with hearing changes (n = 11). Symptoms were present for an average of 16.3 months. The polypoid masses affected the external auditory canal only and ranged in size from 0.4 to 2 cm in greatest dimension (mean, 1.1 cm). Histologically, the tumors demonstrated glands and small cysts lined by a tubuloglandular proliferation of inner ceruminous cells (cerumen-secreting epithelium with decapitation secretion) subtended by a spindled to cuboidal myoepithelial layer. A hyalinized stroma created an infiltrative pattern of growth; surface involvement (n = 8) was seen. Tumors were divided into ceruminous adenoma (n = 36), ceruminous pleomorphic adenoma (n = 4), and syringocystadenoma papilliferum (n = 1) types. The luminal cells were strongly and diffusely immunoreactive with CK7, while the basal cells were highlighted with CK5/6, S-100 protein, and p63. CD117 highlighted the luminal cells preferentially. The proliferation markers revealed a low index. Adenocarcinoma and middle ear adenoma are the principal differential consideration. Surgical excision was used in all patients. Four patients developed a recurrence due to incomplete excision. All patients were without evidence of disease at the last follow-up: alive (n = 28, mean 16.3 years) or dead (n = 12, mean 11.8 years).

Conclusion: Ceruminous gland adenomas are the most common external auditory canal tumors. They demonstrate a dual cell population of basal myoepithelial-type cells and luminal ceruminous (ceruminal) cells. Cerumen pigment, CK7, and p63 can help to distinguish this tumor from other neoplasms that occur in the region. Complete surgical excision results in an excellent long-term clinical outcome.

Key Words: ear, ceruminal adenoma, ceruminous, ceruminoma, immunohistochemistry, prognosis

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Tumors arising from the ceruminal glands of the external ear canal can present a diagnostic dilemma because of their varied clinical and histologic manifestations. While well described in cats and dogs, tumors of this type are rare in humans and therefore are seldom seen by general surgical pathologists.[4,8,27] Further adding to the confusion for pathologists and clinicians alike is the variable nomenclature used to describe tumors of ceruminal gland origin (Table 1). These terms in general do not suggest a specific diagnosis, clinical behavior, treatment alternatives, or long-term clinical outcome. Likewise, many reports in the literature, when critically reviewed, are examples of neuroendocrine adenoma of the middle ear (middle ear adenoma), endolymphatic sac tumors (Heffner tumor), paraganglioma, or most likely represent parotid gland neoplasms that have extended into the external auditory canal.[5,7,10,13,16,17,20,22,25,29,33–38] Many cases are not illustrated or incompletely described histologically, further preventing a critical review. Limited mostly to case reports and small series (Table 2), the English literature is devoid of a large comprehensive evaluation of ceruminous adenomas with respect to their histomorphology, immunohistochemical reactivity, treatment outcomes, and clinical behavior. We undertook this study in an attempt to identify the histologic and immunohistochemical features that can be used to separate benign from malignant ceruminous tumors and to determine the best nomenclature to yield a meaningful clinical management impact.

MATERIALS AND METHODS

The records of 41 patients with tumors diagnosed as ceruminous gland adenoma, ceruminoma, pleomorphic adenoma of ceruminal type, benign mixed tumor of ceruminal gland type, papillary cystadenoma papilliferum, and cylindroma of the external ear canal were selected. The cases were retrieved from the files of the Otorhinolaryngic-Head & Neck Tumor Registry of the Armed Forces Institute of Pathology, Washing-

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TABLE 1. Synonyms for Ceruminous Neoplasms of the External Auditory Canal

Ceruminoma (ceruminomata)
Hidroadenoma
Adenoid cystic carcinoma
Adenocarcinoma of ceruminal type
Mucoepidermoid carcinoma
Syringocystadenoma papilliferum
Pleomorphic adenoma
Ceruminal adenoma
Mixed tumor of skin
Ceruminous adenoma
Cylindroma
Adenoma ceruminalis
Myoepithelioma
Clear cell carcinoma
Aural hydradenoma
Chondroid syringoma
Eccrine cylindroma
Cylindromatous lymphangioma
Cylindromatous deep hidroadenoma

ton, DC, between 1970 and 2000. These 41 cases were chosen from a review of 723 (5.7%) benign or malignant primary ear tumors seen in consultation during this time. Because of the nature of our consultation service, in our total number of cases we were not able to separate tumors arising from the external ear versus external auditory canal in attempting to determine the incidence data. Suffice it to say that ceruminous gland neoplasms are uncommon. Thirty-four cases were obtained from civilian sources, including university medical centers and foreign contributors, 5 cases from military hospitals, and 2 cases from Veterans Administration medical centers.

Materials within the Institute's files were supplemented by a review of the patient demographics (gender, age); symptoms and physical findings and duration at presentation including mass, hearing loss, bleeding, infection, pain, headaches, weakness, syncope or dizziness, nerve paralysis, discharge, equilibrium changes, tinnitus and/or popping, visual changes; and past medical and surgical history. In addition, we reviewed radiographic, surgical pathology, and operative reports and obtained follow-up information from oncology data services by written questionnaires or direct communication with the treating physician(s) or the patient. Follow-up data, available for 40 patients, included information regarding tumor location, presence of recurrent disease, treatment modalities used, and the current patient status. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

TABLE 2. Review of the English Literature (1966 to Present) on Ceruminous Adenomas[1,3,4,6,8,9,14,15,19,21,24,26,28,32,39,41,43]

Characteristic	Value (n = 32)
Gender	
Women	14
Men	18
Ceruminous pleomorphic adenoma	
Women	*3*
Men	*6*
Age (yr)	
Range	12–83
Mean	53.1
Women (mean)	54.4
Men (mean)	52.1
Ceruminous pleomorphic adenoma	*50.5*
Symptom duration (mos)	
Range	1–480
Mean	72.7
Women (mean)	101.3
Men (mean)	46.7
Ceruminous pleomorphic adenoma	*26.9*
Symptoms at presentation*	
Mass	11
Hearing changes	13
Nerve changes (paralysis)	1
Discharge or otorrhea	3
Pain	2
Asymptomatic	9
Location	
Left	12
Right	12
Not reported	8
Size (cm)	
Range	0.5–2
Mean	1.2
Women (mean)	1.3
Men (mean)	1.1
Ceruminous pleomorphic adenoma (mean)	*1.4*
All patients with follow-up (yrs)	23 (4.2)
Follow-up range	0.2–12
Women	12 (4.0)
Men	13 (4.2)
Tumor histology	
Ceruminous adenoma	15 (4.3)
Ceruminous pleomorphic adenoma	6 (3.8)

*Patients may have presented with more than one symptom. Therefore, the numbers do not add up to the total number of patients.

The macroscopic pathology observations noted within this study were gathered from the individual gross descriptions of the neoplasms given by the contributing pathologists. Inked margins of resection were not specifically annotated as we did not perform the prosection. Hematoxylin and eosin-stained slides from all cases were reviewed, with specific histologic features annotated as follows: exact tumor location; lateralization; tumor size (greatest dimension in centimeters); tumor encapsulation (presence or absence); tumor extension (mastoid bone, eustachian tube, and/or middle ear); architectural pattern of growth (solid, papillary, cystic, infiltrating, glandular); dual cell population; surface origin; surface ulceration; presence or absence of necrosis; tumor cellularity (low, moderate, or high); cellular pleomorphism (mild, moderate, severe); presence of nucleoli; mitotic figures (number of mitotic figures per 10 high power fields [magnification at ×40 with a ×10 objective lens using an Olympus BX40 microscope]); atypical mitotic figures (present or absent, and defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms, or indescribably bizarre); ceruminous decapitation secretion; ceroid (yellow to light brown granules in the cytoplasm); and the presence of other microscopic pathologic findings in the remaining tissues.

Immunophenotypic analysis was performed in all cases with suitable material by a standardized Envision method employing 4-μm-thick, formalin-fixed, paraffin-embedded sections. Table 3 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block for each primary tumor. When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 M phosphate buffer, pH of 7.8, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution, pH 6.0 (Citra, Dako Corporation, Carpinteria, CA) and heated for 20 minutes in a steamer. Following this, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded as absent to weak (0 to 1+), moderate (2+ to 3+), and strong (4+) staining, and the fraction of positive cells was determined by separating them into four groups: <10%, 11% to 50%, 51% to 90%, and >90%, especially for the proliferation markers.

A review of publications in English (MEDLINE 1966–2003) was performed, with all cases reported as ceruminous neoplasms (of the external auditory canal) included in the review. Cases that also involved the salivary gland (parotid) or extended into the ear from a tumor "centered" in the oral cavity, nasal cavity, nasopharynx, sinuses, or soft tissues of the neck were excluded.

RESULTS

Clinical

The patients included 19 women and 22 men (Table 4). Their ages ranged from 24 to 85 years, with an overall mean age at presentation of 54.2 years (median, 55 years). The average age at presentation for women was older than men, at 56.6 and 52.1 years, respectively, but there are too few cases to reach statistical significance. There was no difference in demographic information based on adenoma subtype. Patients most frequently presented with a mass lesion in the outer one half of the external auditory canal (n = 33). Other symptoms included hearing changes usually conductive rather than sensorineural (n = 11), nerve changes or paralysis (facial nerve or other cranial nerve involvement; n = 2), and pain (n = 1). Patients occasionally presented with more than one symptom

TABLE 3. Immunohistochemical Panel

Antigen/Antibody	Primary Antibody	Company	Dilution	Cellular Conditioning
Cytokeratin (AE1/AE3 and LP34)	mm	Boehringer Mannheim Biochemicals, Indianapolis, IN, and Dako, Carpinteria, CA	1:50 1:200	Protease digestion
Epithelial membrane antigen	mm	Ventana, Tucson, AZ	Neat	Protease digestion
CK7	mm	Dako	1:400	Protease digestion
CK20	mm	Dako	1:200	Steam
CK5/6	mm	Dako	1:20	None
S-100 protein	rp	Dako	1:800	None
CD117	mm	Dao	1:100	Steam
p53	mm	Dako	1:2400	Steam
p63	mm	Novocastra, Newcastle-upon-Tyne, United Kingdom	1:100	Steam
Ki-67	mm	Immunotech, Westbrook, ME	1:20	Steam

mm, mouse monoclonal; rp, rabbit polyclonal.

TABLE 4. Clinical Characteristics

Characteristic	Value
Gender	
Women	19
Men	22
Age (yr)	
Range	24–85
Mean	54.2
Women (mean)	56.6
Men (mean)	52.1
Symptom duration (mo)	
Range	0–120
Mean	16.3
Women (mean)	23.3
Men (mean)	13.3
Symptoms at presentation*	
Mass	33
Hearing changes	11
Nerve changes (paralysis)	2
Pain	1
Asymptomatic	2

*Patients may have presented with more than one symptom; therefore, the numbers do not add up to the total number of patients.

while there were two asymptomatic patients. By definition, none of the tumors was centered in the parotid gland or developed in patients who had a previous parotid gland tumor. The duration of symptoms ranged from days to 120 months, with an average of 16.3 months. On average, women (mean, 23.3 months) experienced a longer duration of symptoms than men (mean, 13.3 months), a finding without an obvious explanation. In a similar vein, tumors that occurred on the left had a longer mean duration of symptoms than those that arose on the right (17.9 vs. 13.5 months, respectively). Furthermore, when separated by histologic type, the mean duration of symptoms was different: ceruminous adenomas: 17.0 months versus 12.5 months for ceruminous pleomorphic adenomas and syringocystadenoma papilliferum. This may be partially accounted for by the larger size of the latter group. Given the very limited number of cases, statistical analysis could not confirm these differences.

Pathologic Features

Macroscopic

All neoplasms arose in the external auditory canal, and specifically in the outer one third to one half, where the ceruminal glands ("modified" sweat glands) are normally resident (Table 5). Extension into the mastoid bone, middle ear, and base of the skull was not identified. All tumors were unilateral and the majority affected the left side (n = 24). The tumors ranged in size from 0.4 to 2.0 cm, with a mean size of 1.1 cm. The tumors that arose in women were smaller (mean, 1.0 cm) than their male counterparts (mean, 1.2 cm), a curious finding given the inverse differences in duration of symptoms. There was a slight difference in mean size of the tumor when separated by histologic subtype: ceruminous adenomas, not otherwise specified (1.1 cm); ceruminous pleomorphic adenoma and syringocystadenoma papilliferum (1.3 cm). There was no difference in tumor size based on left versus right. As a result of surgical procedures, the tumors were received by the pathologist fragmented into small pieces without an obvious sur-

TABLE 5. Pathology Features

Feature	Value
Location	
Left	24
Right	17
Size (cm)	
Range	0.4–2.0
Mean	1.1
Women (mean)	1.0
Men (mean)	1.2
Ceruminous pleomorphic adenoma (mean)	*1.3*
Growth pattern	
Glandular	37
Infiltrating	11
Solid	6
Papillary	8
Dual population	39
Surface origin	8
Ulceration	3
Mitotic figures (mean per 10 HPF)	0.3
Atypical mitotic figures present	0
Pleomorphism	
Mild	30
Moderate	11
Severe	0
Cellularity	
Low	17
Moderate	20
High	4
Prominent nucleoli	16
Ceruminous decapitation secretion	40
Necrosis present	0
Cerumen/wax granules	36
Associated findings	
Cholesteatoma	2
Dense, sclerotic fibrosis	6

HPF, high power field.

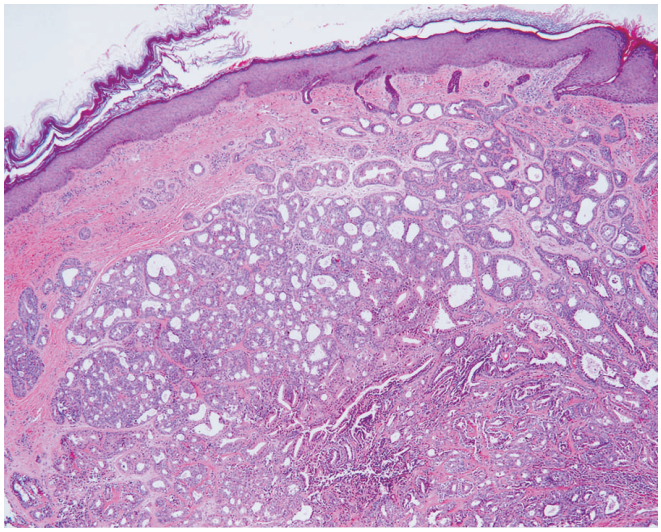

FIGURE 1. Keratinized squamous epithelium overlies a circumscribed although unencapsulated neoplastic proliferation of ceruminous glands. The glandular and small cystic profiles are visible even at low magnification.

face epithelium. However, when intact, the tumors were polypoid. The tumor samples were firm and grayish white to pink. It is important to obtain an accurate location of the biopsy from the surgeon, to exclude glandular neoplasms from the parotid gland or middle ear.

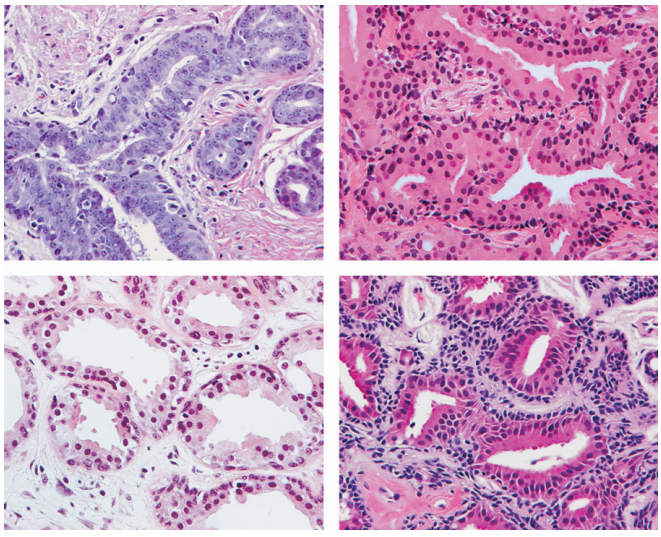

FIGURE 2. A variety of different patterns and histologic appearances of ceruminous adenoma. Stratification of the nuclei with moderate nuclear pleomorphism and a mitotic figure (upper left). Abundant eosinophilic-granular cytoplasm is seen in the luminal cells, which show focal decapitation secretion (upper right). Glandular structures are separated by fibrous connective tissue (lower left). Inner luminal secretory cells subtended by basal myoepithelial cells demonstrate the dual cell population (lower right).

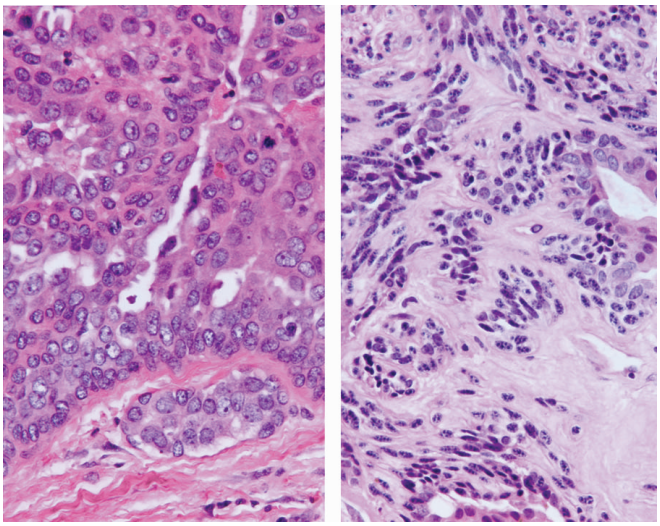

FIGURE 3. A pseudoinvasive growth is seen in areas of fibrosis. Focal nuclear pleomorphism with prominent nucleoli are seen (left). Tumor cell spindling adjacent to more characteristic areas of inner luminal secretory cells (right).

Microscopic

The neoplasms were circumscribed, although a true capsule was not identified (Fig. 1). Surface involvement was identified in a only 8 cases, with surface ulceration in an additional three neoplasm. The neoplasms were divided into three major groups based on specific histologic findings: ceruminous adenoma, ceruminous pleomorphic adenoma, and syringocystadenoma papilliferum.

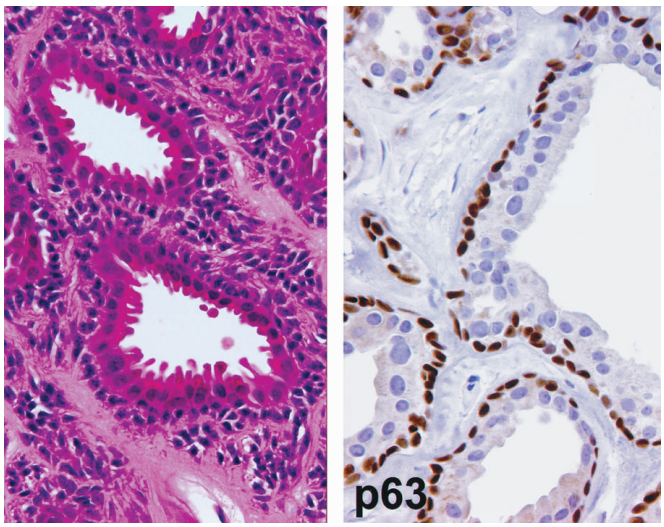

FIGURE 4. Glandular structures show ceruminous decapitation secretion in the luminal cells subtended by a prominent, well-defined myoepithelial cell layer (left). The myoepithelial cell nuclei are accentuated with a p63 immunoreaction (right).

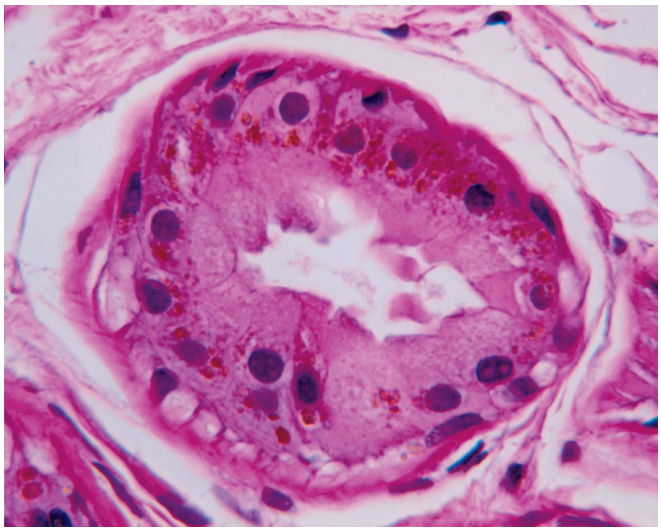

FIGURE 5. Yellow-brown "ceroid" lipofuscin-like material is seen in the cytoplasm are the ceruminous cells, a feature seen in modified ceruminous sweat glands and in ceruminous adenomas.

TABLE 6. Immunohistochemical Panel Results

Antibody	No. (%) of Cases With Positive Reactions
Cytokeratin	22/22 (100)
Epithelial membrane antigen	20/22 (91)
CK7 (*luminal only*)	16/21 (76)
S-100 protein (*basal cell only*)	20/21 (95)
p63 (*basal cell only*)	16/18 (89)
CK5/6 (*basal cell accentuation*)	18/21 (86)
CD117	20/21 (95)
p53 (*<10% reactivity*)	16/18 (89)
Ki-67 (*<5% reactivity*)	14/21 (67)

The ceruminous adenomas contained neoplastic cells that were arranged in a variety of different patterns within a single case as well as between cases (Table 5). Whereas the glandular pattern predominated in most lesions (n = 37; Fig. 2), many of the cases also had cystically dilated spaces. The lesional cells often seemed to "invade" into the surrounding stroma, a feature illustrated more commonly in cases with an interglandular fibrous stroma (Fig. 3). A solid pattern and a papillary pattern were also occasionally identified. All of the ceruminous adenomas and two of four ceruminous pleomorphic adenomas demonstrated a dual cell population composed of a inner luminal epithelial cells subtended by basal/myoepithelial cells adjacent to the basement membrane (Fig. 4). Abundant eosinophilic cytoplasm, arranged in a columnar to cuboidal shape, was seen in the luminal cells. These luminal cells frequently revealed prominent apical caps with decapitation secretion (n = 40) and display well-defined cell borders. Tumor cell spindling may be seen. Many cells also contained golden-yellow-brown pigment cytoplasmic granules (n = 36; Fig. 5). The presence of decapitation secretion and ceroid pigment within the cells assisted enormously in confirming the ceruminal origin of the neoplastic cells. The tumors tended to have a low to moderate cellularity composed of cells with mild to moderate nuclear pleomorphism (Fig. 3).

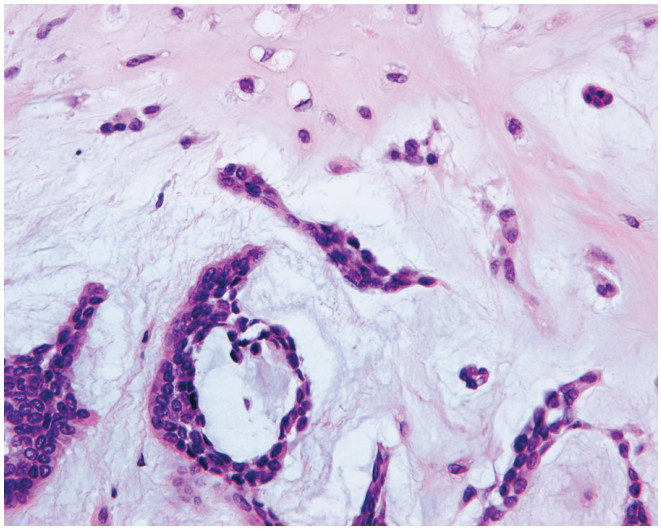

FIGURE 6. The tubules, glands, and myoepithelial cells of a ceruminous pleomorphic adenoma are seen in a loose matrix surrounded by a cartilaginous matrix material (upper field).

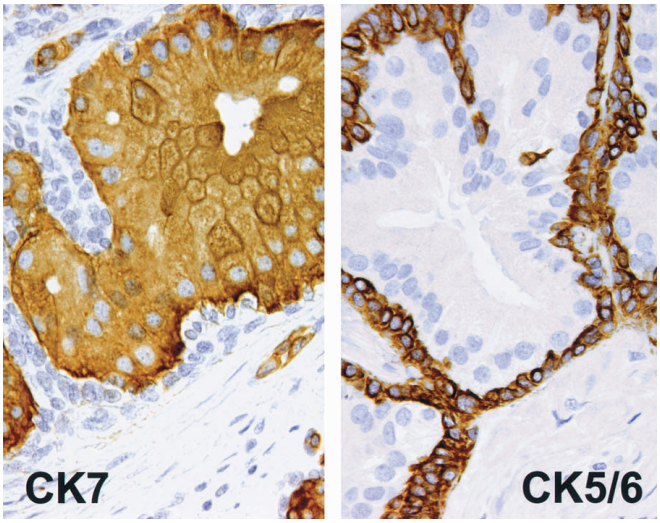

FIGURE 7. Differential immunohistochemical staining highlights the luminal cells (CK7, left) while CK5/6 accentuated the basal cells (right).

Nuclear stratification was sometimes prominent. Nucleoli were focally prominent (n = 16). Mitotic figures were inconspicuous, and atypical mitotic figures and tumor necrosis (not degenerative change) were not observed. Occasional inflammatory cells and areas of dense hyalinization (sclerosis) were seen. Furthermore, an associated cholesteatoma was noted in two cases.

The presence of a more abundant myoepithelial cell population juxtaposed next to areas of increased stroma, specifically mucoid to myxoid-chondroid matrix material, in the presence of ceruminous cells within the "duct-like" structures, confirmed the diagnosis of a ceruminous pleomorphic adenoma (Fig. 6). The ceruminous decapitation secretion and ceroid pigment was identified within the luminal cells of the poorly formed duct and tubule structures of the pleomorphic adenomas. Nuclei were generally pale staining and eccentrically located, with small nucleoli. Mitotic figures were essentially absent. Only a single case of a syringocystadenoma papilliferum was diagnosed, with the characteristic papillary projections into a cystic lumen, lined by a dual cell population of benign-appearing cells.

Immunohistochemistry

All lesions tested reacted strongly and diffusely with a keratin cocktail (Table 6). Where the surface epithelium was present, it was strongly and diffusely immunoreactive for the epithelial markers analyzed and served as an internal quality control. The majority of cells exhibited weak and focal reactivity with epithelial membrane antigen (91%). The dual cell population was accentuated by the immunohistochemical studies. The luminal cells were strongly immunoreactive with cytokeratin 7 (CK7) (Fig. 7) and while these same cells were weakly CD117 reactive. The basal-myoepithelial cells were strongly and diffusely reactive in both the nucleus and cytoplasm with S-100 protein (95%), in the cytoplasm only with CK5/6 (86%; Fig. 7), and in the nucleus only with p63 (89%; Fig. 4). Sixty-seven percent of cases tested demonstrated Ki-67 immunoreactivity ranging from 2+ (n = 13) to 3+ (n = 1) but affected <5% of the nuclei in the specimen, with the majority affecting ≤1%. p53 was identified in 89% of cases; although immunoreactivity ranged from 1+ to 3+, <10% of the nuclei in the specimen were affected in 12 cases, while 4 cases demonstrated reactivity in about 30% of nuclei.

Treatment and Follow-up

All patients were treated by partial or complete surgical excision; complete surgical removal of the tumor was frequently impossible as a result of the complex anatomy of the ear and temporal bone. No patients received adjuvant chemotherapy or radiation therapy. Follow-up data were obtained in 40 patients (Table 7). One foreign patient was lost to follow-up. Of these 40 patients, none had evidence of disease at the last follow-up (mean, 14.9 years); 28 patients were alive without evidence of disease (mean follow-up, 16.3 years); 12 patients had died of unrelated causes without evidence of disease (11.8 years). However, 4 patients had developed a recurrence. Of the 4 patients with recurrence, 2 had a wider excision performed at 2 and 6 months, respectively. Perhaps these tumors could be considered residual disease rather than recurrent disease, but it is difficult to make such a distinction given the anatomic restrictions of the area and the fact that we are a referral institution (ie, total gross excision was unknown). The other two patients developed local recurrences in the same site as the previous tumor between 2 and 4 years after the initial presentation. After surgical excision, both patients are free of disease at the last follow-up. There was no difference in overall patient outcome or length of follow-up between the patients who developed a recurrence and those who did not. Further, there was no difference in outcome between men and women, nor between the different types of histology.

TABLE 7. Patient Outcome (mean years of follow-up)

	All Patients*	A'NED	D'NED
All patients with follow-up	40 (14.9)	28 (16.3)	12 (11.8)
Follow-up range	2.2–28.2	2.2–28.2	1.6–24.2
Patients with recurrence	4 (21.4)	2 (24.5)	2 (18.5)
Men	21 (13.6)	17 (14.8)	4 (8.8)
Women	19 (16.4)	11 (18.7)	8 (13.5)
Tumor histology			
Ceruminous adenoma	35 (14.9)	25 (16.3)	10 (11.4)
Ceruminous pleomorphic adenoma	4 (16.8)	3 (16.3)	1 (18.1)
Ceruminous papillary cystadenoma	1 (9.5)	n/a	1 (9.5)

A'NED, alive, no evidence of disease; D'NED, dead, no evidence of disease; n/a, not applicable.
*One foreign patient was lost to follow-up.

DISCUSSION

The normal external ear canal is an S-shaped passage measuring about 2.5 cm, lined by a very thin squamous mucosa covering scant fibrous stroma containing both sebaceous and modified ceruminous sweat glands—ceruminous glands. The ceruminal glands are deep within the dermis, usually close to the cartilage, which is present in the outer one third to one half of the canal. The inner bony portion of the canal does not contain ceruminal glands. The ceruminal glands are comprised of columnar cells containing intensely eosinophilic cytoplasm, frequently displaying "apical caps," "secretory snouts," or "blebbing." These cells are surrounded by a layer of myoepithelial cells. By definition, ceruminous cells lose part of their cytoplasm during secretion, different from the holocrine sebaceous glands, which lose all of the cell as part of the secretion. Ceruminous glands are typical ceruminous sweat glands with a watery fluid secretion devoid of lipids. This fluid drains into ducts, which open, along with the sebaceous gland ducts, into the hair sacs of the fine hairs in the ear canal. This fluid mixes with the "secretion" of the sebaceous glands to create cerumen (wax). The luminal secretory cells contain cytoplasmic golden yellow-brown, water-insoluble lipoprotein pigment granules, similar to ceruminous glands elsewhere, although these pigment granules do not become part of the secretion.[6,19,20,26,32,42] These granules are periodic acid-Schiff positive, Sudan black positive, and also stain with the Ziehl-Neelsen acid-fast method. The presence of this yellow-brown granule confirms the ceruminous nature of the neoplasm, but it does not necessarily confer a unique designation to the tumor. Eccrine sweat glands are not present in the external auditory canal. While histogenesis is difficult and unsettled, the presumptive progenitors for ceruminous adenomas include embryonal anlage, ectopic remnants of salivary gland, and the ceruminal gland itself.

The persistent use of unsuitable terms pertaining to ceruminous (ceruminal) tumors in the literature[1,3,4,6,8,9,12,14,15,18,19,23,24,26,28,32,34,39,41,43] has caused considerable confusion, resulting in incorrect classification and inappropriate therapy when applied in daily practice. While it is not the purpose of this study to resolve taxonomic issues or to specifically posit nosological preferences, a comment is necessary to assist the pathologist and clinician alike in implementing uniform nomenclature (Table 8).

Ceruminous adenoma is classified as "a well differentiated, benign neoplasm, localized, occasionally cystic and showing papillary proliferation of glands histologically similar to normal ceruminous glands."[42] Retention of the generic term "ceruminoma" to encompass all tumors of ceruminous origin has been strongly advocated by some authors for ceruminous tumors arising from the external auditory canal, while others ardently dissent to the use of this nondiscriminating term. Indeed, "ceruminoma" and "cylindroma" have been used to describe both histologically benign and malignant neoplasms, thereby providing the clinician and surgeon with little value and no guidance as to management and follow-up. The continued use of these terms (ceruminoma and cylindroma) is discouraged.[16,20,26,30,31,34,42] Hidradenoma had gained ground in some circles since the ceruminous neoplasm arises from a modified ceruminous sweat gland, yielding a histologically inseparable neoplasm from those that arise from sweat glands elsewhere (nipple, axilla, perianal, and genital areas).[20,28,39] Other modified ceruminous sweat glands are seen in the eyelid (Moll's glands) and mammary glands. Interestingly, no specific histochemical differences in these neoplasms between the different anatomic sites of origin have been identified.[6,22,39] However, malignant neoplasms of ear origin are far more frequent than ceruminous malignancies of these other anatomic sites.[9,19,24,42] While there is nothing inherently incorrect with the term hidradenoma, its use is not accepted by otorhinolaryngologists and head and neck surgeons. Pleomorphic adenoma (mixed tumor) is separately described as a neoplasm "forming strands and nests of epithelial cells in a myxoid, pseudocartilaginous, or hyaline stroma which contains mucin."[42] These tumors are even more uncommon, but the term ceruminous pleomorphic adenoma is advocated to designate the anatomic location (external auditory canal) and the histologic classification. Only occasional mention is made of syringocystadenoma papilliferum in this anatomic site, but adding "ceruminous" will aid in the correct classification.

There is a wide range of adverse agents from noisy environments to pathologic conditions that may cause serious functional disturbances. Unfortunately, no known etiologic agent has yet been identified that results in ceruminous adenomas. The neoplasm is most uncommon and is in fact rare. Difficulties in nomenclature aside, there are not many reported cases in the literature (Table 2). Despite the referral nature of the Armed Forces Institute of Pathology, ceruminous adenomas (all types) comprise only 5.7% of all ear (pinna) and external auditory canal neoplasms. Others have suggested an even lower frequency, which is probably most likely.[9,19,24,42]

TABLE 8. Nomenclature for Ceruminous Neoplasms of the External Auditory Canal

Benign Neoplasm	Malignant Neoplasm
Ceruminous adenoma	Ceruminous adenocarcinoma
Ceruminous pleomorphic adenoma	Ceruminous adenoid cystic carcinoma
Ceruminous syringocystadenoma papilliferum	Ceruminous mucoepidermoid carcinoma

Any age can be affected, with a range from 12 to 85 years, although the mean age at presentation is 52 to 54 years. While patients with ceruminous pleomorphic adenoma are younger at initial presentation (mean, 50.5 years), there are too few cases to perform a valid statistical analysis. There is a difference in age at clinical presentation between patients who have benign ceruminous tumors (mid 50s) than those who present with ceruminous adenocarcinomas (mid 40s).[2,9,19,24,42] No gender predilection exists for the whole group, although there may be a slight gender bias toward men with ceruminous pleomorphic adenoma (8:5), contrary to suggestions in individual case reports.

Ceruminous adenomas produce very few symptoms and in general they are nonspecific, related to the size of the mass and the degree of canal obstruction. Hearing loss, nerve changes (including paralysis), aural discharge, mild to moderate otalgia (earache, pain), and rarely bleeding will accompany a mass lesion in most patients.[2,9,19,24,42] Pain is a useful clinical feature, which can alert the surgeon to be more suspicious of a malignant tumor, especially if difficulties are encountered in the histologic classification. However, pain can be encountered in both benign and malignant ceruminous neoplasms. Asymptomatic discovery during examination for other reasons is also frequently described. The interval between the first appearance of symptoms and seeking medical attention ranges up to 480 months, although most patients have symptoms for a number of years.

It is imperative to document the exact anatomic location. Ceruminal glands are normally resident in the outer one third to one half of the external auditory canal overlying the cartilaginous region. Ceruminal glands are not present within the middle ear, nor have they been ectopically identified in this location.[8] Even though an adenoma can fill the external auditory meatus, an intact tympanic membrane is nearly always identified. A "glandular" type neoplasm within the middle ear needs to be considered a neuroendocrine adenoma of the middle ear (NAME)[40] or middle ear adenoma until it is proved otherwise. Similarly, a pleomorphic adenoma of the parotid gland may extend into the external auditory canal. Radiographic studies can help to "center" the lesion, but if a mass "behind" the ear, in the "pre-auricular" space, or within parotid gland parenchyma is identified, it should be diagnosed as a salivary gland neoplasm. These specific anatomic site concerns will allow for appropriate clinical management for the true lesions (NAME and parotid pleomorphic adenoma).

The macroscopic structure of the tumor varies considerably, but a polypoid mass of a red to tan appearance is most characteristic, with a cut surface occasionally containing small cysts. Surface ulceration occurs in a minority of cases.[9,19,24,41,42] Most of tumors are small (mean, 1.15 cm) probably due to the confines of the anatomic location. Curiously, the ceruminous pleomorphic adenoma cases tend to be slightly larger (mean, 1.4 cm).

Ceruminous adenomas are composed of well-differentiated tubular, ductal, or papillary structures reminiscent of ceruminous glands. Two distinct cell layers are easily identified in most cases. The luminal, columnar, secretory cells contain ceroid pigment and display apical secretion by decapitation. Invasion, perineural growth, profound nuclear pleomorphism, mitotic activity, tumor necrosis, and hemorrhage are not observed.[9,19,24,42] Ceruminous adenoma is separated from ceruminous PA, which is a benign mixed tumor demonstrating ceruminous differentiation, including ceroid pigment within the cytoplasm. This ceruminous adenoma type is quite uncommon, although syringocystadenoma papilliferum is probably as rare.[3,6,8,18,19,24,30,32,39] The glistening, myxoid cut surface during macroscopic examination may give a hint of the diagnosis to come. The duct-lining epithelial cells blend with the surrounding myoepithelial cells that are embedded in the myxochondroid matrix material. The ceruminous type of pleomorphic adenoma seems to have a more variegated and haphazard tissue pattern, with significant variability in the size and shape of the glandular-tubular structures when compared with primary salivary gland neoplasms. Fat has been described in ceruminous pleomorphic adenoma,[39] whereas axiomatic, parotid tissue must not be part of the neoplastic proliferation for a designation of ceruminous PA. Also, there is some similarity with integumentary ceruminous fibroadenoma, but the lack of hyperplastic epithelium and fusion of the cords and ducts should help with the distinction.

Ceruminous syringocystadenoma papilliferum is quite rare, but the unique papillary architecture with rich inflammatory (plasma cell) infiltrate is sufficiently unique in this location to be accurately diagnosed without difficulty.

It is always curious to see how quickly recently developed sophisticated methods or antibodies are adopted to separate neoplasms. The differential immunohistochemical staining of the inner luminal cells and the outer basal/myoepithelial cells is occasionally of value in a tumor that demonstrates a more solid growth or where the basal cells are inconspicuous. While CK5/6 and S-100 protein are quite satisfactory in highlighting basal cells,[8,24] the strong and diffuse nuclear reaction with p63 is perhaps easier to interpret, especially in small biopsy specimens that have suffered from crush or electrocautery artifact. The immunohistochemical analysis is identical to those of normal ceruminal glands, supporting the histogenesis of this benign neoplasm.

The differential diagnosis of ceruminous adenoma (all types) includes ceruminous adenocarcinoma, neuroendocrine adenoma of the middle ear (NAME; middle ear adenoma), parotid pleomorphic adenoma (benign mixed tumor), meningioma, and paraganglioma, although the separation from ceruminous adenocarcinoma may be the most difficult. It has been suggested that ceruminous adenocarcinomas are more frequent than ceruminous adenomas in the external auditory canal.[4,6,9,11,16,19,24,33,34] Ceruminous adenocarcinomas demon-

strate significantly more infiltration, perineural invasion, irregular gland formation, pleomorphism, prominent nucleoli, increased mitotic figures, atypical mitotic figures, and tumor necrosis. Unfortunately, in the aggregate these features are quite helpful, but adenocarcinomas generally have only a few of these features, blurring the line of separation, made especially worse in a small biopsy specimen. Perineural invasion is probably most helpful in separating adenoma from carcinoma, but it is an infrequent feature in carcinoma (specific but not sensitive), as is the presence of tumor necrosis. Curiously, the brown ceroid pigment granules are generally absent in adenocarcinomas.[6,16]

Chemodectoma and paraganglioma (sometimes the terms are used interchangeably) usually have a characteristic angiographic appearance, while histologically they are composed of a nested pattern of paraganglia cells supported by a network of sustentacular cells. The chromogranin and S-100 immunohistochemical studies will help to confirm the diagnosis.

The delicate and complicated structures of the ear are located in a comparatively inaccessible part of the skull and are well protected by some of the densest bone formation in the body. Understanding the specific anatomy and histology of the ear allows for accurate diagnosis and treatment of the conditions that affect this area. Therefore, to say "complete surgical excision" is the treatment of choice raises the specter about adequacy of resection and what amount of normal tissue around the neoplasm should be taken. The adequacy of the initial biopsy goes a long way to resolving this problem. However, many biopsies are small "incisional" rather than "excisional" biopsies and may not adequately represent the periphery of the tumor. Given the "infiltrative" nature of the neoplasm, conservative re-excision is recommended for any ceruminous adenoma diagnosed by an "incisional-type" biopsy. If, after careful scrutiny of the biopsy, there is any question about the total removal of the neoplasm, clinical follow-up is suggested as recurrences may develop in incompletely removed tumors. Radiation and chemotherapy are not used for these benign neoplasms.[9,19,24,42]

In summary, ceruminous tumors of the external auditory canal can be divided into benign and malignant neoplasms, with the benign neoplasms developing two unique subtypes: ceruminous pleomorphic adenoma and ceruminous syringocystadenoma papilliferum (Table 8). The unique architecture and histology of these neoplasms allow for their separation from other neoplasms in this area (squamous cell carcinoma, paraganglioma, NAME, meningioma), which contributes to appropriate clinical management of these benign tumors.

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