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REVIEW

Ceruminous adenoma of external auditory canal

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ABSTRACT

INTRODUCTION: Tumors of the external auditory canal are very rare in humans. Many cases are described within the animal genus. There is no sex difference, and the age of presentation is very variable. Thanks to the new classification (WHO – 4th edition), ceruminous adenomas of the external auditory canal have been introduced. These are benign tumors of apocrine glandular cell characteristics without signs of malignancy.
EVIDENCE ACQUISITION: We conducted a systematic review to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in order to evaluate the incidence of cases in the literature, symptoms, diagnostic criteria, therapeutic choices and the follow-up of this benign lesion. Seventeen literature articles were considered.
EVIDENCE SYNTHESIS: In all cases, the ceruminous adenoma manifested itself in an asymptomatic or paucisymptomatic manner, with symptoms related to the encumbrance of the mass. Instrumental diagnostics (computed tomography and magnetic resonance imaging) excluded the invasion of the surrounding noble structures. The treatment choice is surgical, by complete excision with surrounding healthy tissue. The histological diagnosis is confirmed by immunohistochemistry (CK 5-7; S-100).
CONCLUSIONS: Even though it is a benign tumor, it is possible to have recurrences or transformations into a malignant tumor years later, especially when there are no free margins after excision. For this reason, follow-up over time of the lesion is recommended, especially in the case of incomplete excision. There are no indications for adjuvant therapy.

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KEY WORDS: Adenoma; Ear; Neoplasms; Immunohistochemistry.

Introduction

Tumors originating from the ceruminous glands of the external auditory canal (EAC) are quite frequent in the animal world (especially cats and dogs) but equally rare in humans.[1, 2] It is estimated that they represent approximately 0.00025% of all tumors and 2.5% of tumors affecting the ear.[3] Its manifestation is more frequent around the sixth decade of life, with an interval between 25 and 80 years, without sex differences.[2]

Currently, for the classification of ear tumors, reference is made to the 2017 Classification of Head and Neck Tumors. Ceruminous tumors affecting the external ear are introduced into this classification. Tumors of these modified apocrine sweat glands are characterized by: a basal myoepithelial bilayer surrounding the secreting cells facing the glandular lumen. We distinguish adenomas and adenocarcinomas.[3, 4] Table I summarizes the tumors dividing benign from malignant.

Clinically, most patients are asymptomatic or present symptoms related to the mass effect of the tumor such as sensation of obstruction of the duct, hearing loss, itching. Other symptoms such as otorrhea or pain are generally secondary to the lesion, due to bacterial superinfections. The growth of benign tumors is generally very slow, as in the case of low-grade malignant tumors. However, due to involvement of surrounding structures, in malignant forms the pain appears earlier.

TABLE I.—*Classification of ceruminous neoplasms of the external ear.*

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

Malignant tumors are characterized by the early onset of pain due to the involvement of surrounding nerves, otorrhea and bleeding. For this reason, radiological evaluation with computed tomography (CT) and magnetic resonance imaging (MRI) is very important to evaluate the extension of the tumor, the involvement of the middle ear and the surrounding bone and cartilaginous tissue.[5]

Immunohistochemistry is very important for diagnostic purposes. In fact, the cells of the basal layer are positive for various types of keratins. The luminal cells are instead positive for CD 117, MUC1, CK 7 and 9; while myoepithelial cells express S100, p63, CK5/6 antigens.[1]

The immunohistochemical investigation is extremely useful. In fact, in the literature there are reports of cases of neuroendocrine adenoma of the middle ear or parotid adenoma, with extension to the external auditory canal where the careful histopathological examination allowed the lesion to be correctly identified and classified.[6-8]

Since these are benign tumors, the surgical treatment of choice involves excision of the lesion.[9]

Evidence acquisition

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] The study was carried out in accordance with the principles of the Helsinki Declaration, and an informed consent was obtained from our participant before including him in the study. No review protocol was registered for this study.

Manuscripts were screened primarily by Ovid Medline and EMBASE and from other sources (PubMed Central, Web of Science, Cochrane review and Google Scholar) and published from January 1950 to August 2023. Literature searches were performed in September 2023. The search was conducted in PubMed with the last search taking place on October 1, 2023. The words searched for on PubMed are: "ceruminous adenoma" OR "pleomorphic adenoma" and "external auditory canal."

In the preliminary phase, the abstracts of the works were analyzed after eliminating duplicates. Only works in English that concerned the external ear were taken into consideration. Reviews and articles concerning ceruminous adenoma found in animals were excluded.

Two authors (MM, PC) independently performed the first selection of articles. A third author (SA) resolved conflicts between the two first reviewers. Any missing data were obtained by contacting the authors of the study.[11] At the end of the selection, the reported cases were selected by authors, year of publication, number of patients, age of patients, sex, location and type of tumor, recurrence and secondary treatment.

Our research after removal of duplicates and considering only ceruminous adenomas of the EAC focused on 109 studies. We excluded 55 articles who talked about tumors affecting animals. The subsequent exclusion of articles due to the above criteria led to the definition of 17 articles. We summarized the included studies in Figure 1.

The aim of this review was to understand the different presentation modalities, the diagnostic criteria used, the results obtained from the histological examination and the importance of immunohistochemistry to confirm the diagnosis, the surgical techniques used and the necessary follow-up period to exclude the possible persistence or transformation of the neoplasm into a malignant

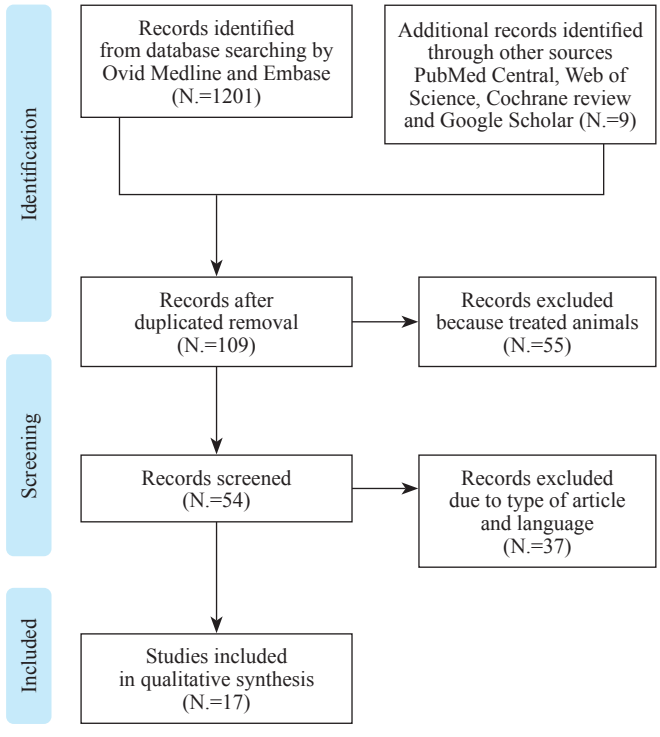

Figure 1.—PRISMA flow diagram of the systematic search.

tumor. Below we report the experiences of the authors who have described cases of ceruminous adenoma in the literature.

Evidence synthesis

Leitner[12] described the case of a 65-year-old woman with a red lentil-like mass inside the right EAC. The lesion was excised in two stages due to the difficulty during the first surgery in the exposure. Already ten days after the first operation the persistence of the disease was clinically evident. The histological examination indicated a ceruminous adenoma. This study demonstrates how, even though it is a benign neoplasm, correct excision avoids the risk of recurrence.

Cankar *et al.*[13] analyzed 7 cases, 5 men ed 2 women aged between 27 and 76 years old. In one of the cases studied, the discovery of a growth affecting the ear canal was completely random as there were no symptoms reported by the patient. Two patients had come to the attention of the ear specialist due to hearing loss. One patient complained of intermittent pain; one patient had a diagnosis of otitis externa, while another had had a pimple for approximately 7 years. In 5 patients, a polypoid-like or granulomatous lesion was found at the visit and was removed under local anesthesia. The histological examination highlighted the presence of a ceruminous adenoma of the EAC. In fact, neoplastic glandular cells were highlighted immersed in an abundant stroma with squamous epithelium free of atypia. For these patients, a follow-up of approximately 1 year was performed, with subsequent voluntary abandonment by the same patients.

In two other patients the lesions affecting the external ear turned out to be an adenocarcinoma of the ceruminous glands and a cylindroma. This required more destructive surgeries. In one of the cases there was a recurrence of the disease two years after the first operation. No follow-up data is available for both. The patients are presumably deceased. We considered only five cases in our review with ceruminous adenoma gland type diagnosis.

Lynde *et al.*[14] described seven cases, in particular, the case of a 31-year-old man with accidental discovery of asymptomatic mass in the right EAC. He was treated with excision in local anesthesia. Histological examination showed ceruminous adenoma. After 4 years, the patient presented recurrence treated with radiant therapy (5000 rads in 33 days). Six years later, he had a new recurrence in right EAC. No preliminary radiological investigations were performed; we have no information on immunohistochemical typing. It is the first described case of recurrence even after radiotherapy. Other six cases were not taken into consideration for our review because three patients were affected by adenocarcinoma and three other patients by adenoid cystic carcinoma involving both the EAC and the middle ear.

Yamamoto *et al.*[15] described the case of a 55-year-old man with right facial spasm without paralysis. He reported no ear pain, no otorrhea, or hearing loss. Otoscopy revealed a small hard-elastic formation at the level of the superior wall of the EAC. The CT scan showed a mass at the level of the posterosuperior wall of the EAC which was related to the tympanic membrane without invading it and did not alter the surrounding bone. The tumor was removed under general anesthesia *via* a retroauricular approach. Histological examination showed apocrine cells without mitotic alterations indicative of malignancy. The final diagnosis was ceruminous adenoma. In conclusion, this is an occasional finding as the facial spasm, given the benignity and well-defined localization, was not related to the tumor. No recurrence was observed after 14 months.

Tang *et al.*[16] described the case of a 39-year-old man who reported hearing loss due to a growth of approximately 2 cm at the EAC level. The lesion was excised under local anesthesia. Histological examination showed glandular apocrine cells with surrounding myoepithelial component. Immunohistochemistry was positive for CK, vimentin, α-smooth muscle actin and vimentine, according to ceruminous adenoma. No recurrence was registered after one year.

Gerber *et al.*[17] described the case of a 47-year-old man with a growing mass in right EAC from six months. In the last two weeks the patients referred otalgia. The preoperative investigations were MRI – which described the absence of invasion of the surrounding structures – and fine needle aspiration cytology (FNAC). The presence of crystalloids, a low number of cellular atypia and rare mitoses allowed the benign tumor to be differentiated from adenocarcinoma. For this reason, the use of FNAC, together with clinical history and imaging, is very useful for the correct classification of the patient and the therapeutic process. The lesion was excited in local anesthesia and the patient underwent 15 months of follow-up. Histological examinations confirmed the diagnosis of ceruminous adenoma gland type.

Elsuler *et al.*[18] described the case of a 37-year-old woman who referred painful mass in left ear. The initial diagnosis was furunculosis, which was treated with drainage of the lesion and antibiotics. Due to the failure of the

treatment, a CT scan was performed showing a large mass in left external auditory canal without bone invasion. The lesion was completely excised, and the patient underwent 12 weeks of follow-up with no evidence of persistence or recurrence of disease.

Markou *et al.*[19] described the case of a 6-year-old woman with an exophytic mass in left ear with sporadic otalgia, tinnitus and hearing loss. The clinical absence of symptoms and the presence of what appeared to be a polyp led the specialists to the diagnosis of chronic otitis media. However, in recent months, the symptoms had become persistent, and the "polyp" was also visible externally.

Magliulo *et al.*[20] described the case of a 5-year-old man with right EAC mass who caused intermittent serous otorrhea. The lesion was completely excised with transmittal approach and histological examination was characterized by well differentiated localized neoplasm with papillary proliferation of ceruminous gland, showing diagnosis of ceruminous adenoma. No recurrence was observed after one year.

Maranhao *et al.*[21] described the case of a 27-year-old woman with a diagnosis of left external auditory mass identified like ceruminoma (ceruminous adenoma). After 10 years, MRI showed a heterogeneous mass in the left temporal bone who caused prosopagnosia, hemiglossoplegia, ipsilateral deafness. Due to the symptoms and the results of the investigations, the patient underwent radiotherapy. This is a rare case of ceruminous adenoma with recurrence and transformation into a malignant neoplasm. There are no data regarding histology and any immunohistochemistry performed. CT and MRI demonstrated the presence of a formation occupying the EAC with involvement of the mastoid wall. No invasion of brain structures or parotid gland was observed. For this reason, the patient was first subjected to an incisional biopsy and subsequently to surgery with mastoidectomy to excise the lesion. Histological examination showed the presence of glandular-type neoplastic epithelial cells on a base of myoepithelial tissue. Immunohistochemistry was positive for CK7 and S-100 protein. This result allowed the diagnosis of ceruminous adenoma. No recurrence was reported during follow-up.

Niemczyk *et al.*[22] described the case of a 3-year-old man who presented left skin lesion in the preauricular, temporozygomatic, submental and buccal region and lesion in left EAC caused itching. Histological examination revealed that skin lesion was an epidermal papillary nevus. In the same patient a ceruminous adenoma coexists in left EAC. No recurrence was described after six months. This is the case of the youngest patient affected by ceruminous adenoma treated with surgery.

Psillas *et al.*[23] described a case of an 87-year-old woman with left otalgia, yellowish discharge, itching, and hearing loss. The physical examination revealed the presence of a soft-looking mass at the EAC level which, after pressure, secreted a yellowish liquid. There was a concomitant perforation of the tympanic membrane. CT and MRI excluded involvement of bone and surrounding structures. However, the presence of a parotid lymph node was noted. FNAC excluded the presence of malignant cells. Lesions were removed by using a transmittal approach in general anesthesia. Macroscopically, the lesion appeared completely excised and covered by capsular connective tissue. Histological examination highlighted the presence of ceruminous apocrine cells immersed in a myxoid stroma. Immunohistochemistry showed positivity for keratins 5/6/7, S100 protein, and p63. This confirmed the definitive diagnosis of ceruminous adenoma. No recurrence was observed after 2 years.

Jaber *et al.*[24] described the case of a 55-year-old man who referred hearing loss and occasional bleeding from the right ear. The physical examination highlighted a mass that occluded 1/3 of the right EAC without alterations of the tympanic membrane. Preoperative CT did not show bone tissue invasion. The lesion was excised using a retroauricular approach. Histological confirmation of ceruminous adenoma gland type occurred thanks to immunohistochemistry (positivity for CK 7). The patient underwent follow-up for 6 months.

Shen *et al.*[25] described the case of a 78-year-old man with 6 months of right otorrhea. Otoscopy revealed a pink, hard elastic mass implanted at the level of the right EAC. CT showed a soft lesion without signs of bone erosion. The lesion was completely removed by transmittal approach under local anesthesia. Histological examination showed apocrine glandular cells immunohistochemically positive for CK, α-SMA, desmin, S-100 protein, Glut-1, HIF-1α, PI3K and p-Akt. No recurrence was observed after 27 months.

Uz *et al.*[2] described the case of a 32-year-old man with otorrhea, otalgia, and hearing loss. Otoscopy revealed a mass of soft contents occluding the duct. The tonal audiometric examination showed a conductive hearing loss of approximately 25 dB. CT confirmed the objective picture excluding bone involvement. A non-diagnostic FNAC was performed due to the scarcity of available cellular material. The lesion was completely removed under local anesthesia. The histological examination highlighted a double cellular component: one glandular, one epithelial; without pathological mitotic alterations. The final diagnosis was ceruminous adenoma. No recurrence was described after one year.

Ramli *et al.*[26] described the case of a healthy 34-year-old woman with progressive right hearing loss from two years. Otoscopy revealed a non-bleeding, non-pulsating mass at the superior wall of the right EAC. The audiometric examination showed a conductive hearing loss on the right due to the encumbrance of the mass. The CT scan highlighted the presence of a mass implanted on the upper wall of the EAC with slight bone erosion, without involvement of the middle ear or of the other surrounding nervous structures. The lesion was removed *en bloc* under general anesthesia with drilling of the reworked bone. Histological examination showed cuboidal and spindle-shaped apocrine cells surrounded by myoepithelial cells. Immunohistochemistry showed positivity for CK7. No recurrence was observed after one year.

Nishimura *et al.*[27] described the case of a 70-year-old woman with a history of right EAC mass which caused itching. The lesion was excided in local anesthesia. Histological examination showed ceruminous adenoma characterized by glandular proliferation with myoepithelial cells positive to CK5/6. Lesion was completely excised. After 2 years and 9 months there was a recurrence on the posterior wall of right EAC. TC and MRI did not show invasion of bone or near tissues. Mass was excited *en bloc* in general anesthesia. Histological examination showed chondromyxoid stroma around myoepithelial cells and apocrine cells. For these reasons, the tumor was diagnosed as ceruminous pleomorphic adenoma (CPA), an unusual variant of CGA.

Supplementary Digital Material 1 (Supplementary Table I)[2, 12-27] resumes articles included in qualitative analysis and summarized results.

Institutional representative case

In September 2023, a 64-year-old man arrived at the ENT Unit of the Federico II University Hospital in good general condition due to a soft lesion at the left EAC level. This lesion had already been found in a previous ENT specialist visit during 2014. The lesion appeared small and specialist follow-up was recommended. The patient did not complain of pain or otorrhea; however, he reported partial occlusion of the ear canal upon palpation and mild subjective hearing loss. The otoscopic examination highlighted a cystic lesion that completely occluded the left EAC (Figure 2). The tonal audiometric examination revealed a mild sensorineural hearing loss on the right, mixed mainly conductive on the right. CT showed: left EAC completely obliterated by a mass with an oval appearance, of soft tissue density, with a maximum diameter of approximately 17 mm which bordered the ipsilateral tympanic membrane and integrated the ossicular chain and the surrounding bone component (Figure 3).

The lesion was excised *en bloc* with anesthesia and transmittal access; so, the skin of the duct was reconstructed with skin flaps. A small pad was placed to support the EAC which was subsequently removed on the seventh day.

The definitive histological examination highlighted a tumor lesion with characteristics compatible with apocrine adnexal derivation. The lesion was characterized by the presence of an internal epithelial layer and an external myoepithelial layer. There were no nuclear alterations or pathological mitotic activity. Immunohistochemistry was positive for CK 7; while α-SMA was in agreement with the diagnosis of ceruminous adenoma of the external auditory canal (Figure 4). No recurrence was reported three months after surgery (Figure 5). The patient is currently under follow-up with monthly otoendoscopic checks.

Discussion

It is known that the external auditory canal contains both sebaceous glands and ceruminous glands, which are considered modified apocrine glands. Both glandular components contribute to the formation of earwax which has a very important antimicrobial function. From histological

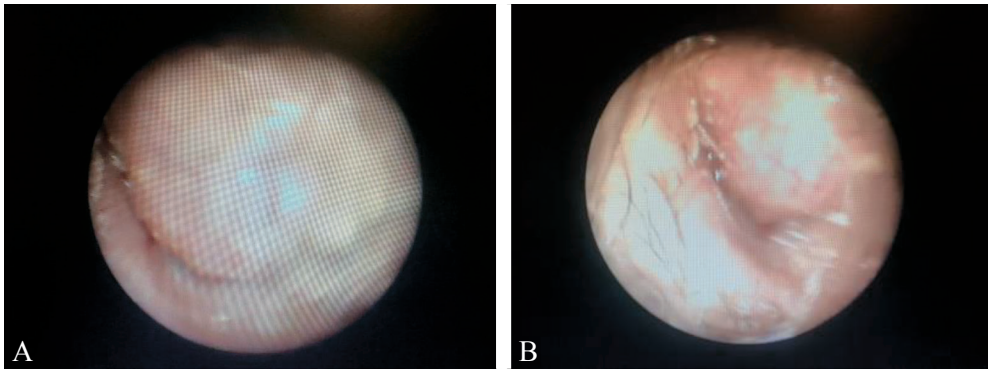

Figure 2.—A, B) Cystic lesion that completely occluded the left EAC. EAC: external auditory canal.

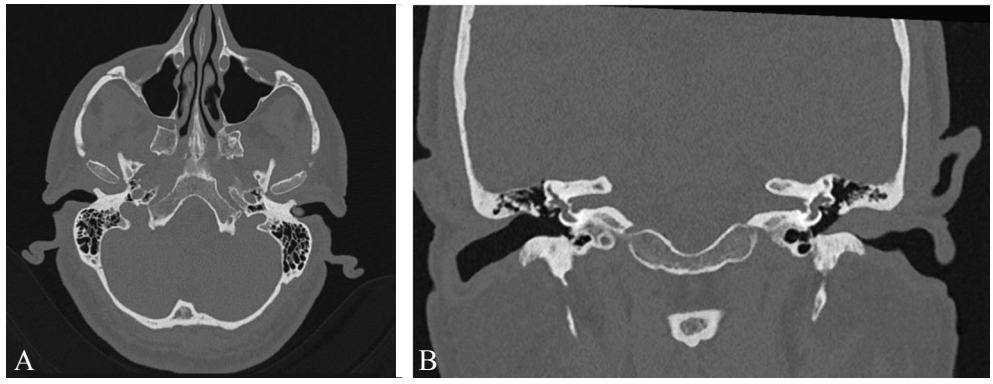

Figure 3.—CT scan examination: A) axial view; and B) coronal view. CT: computed tomography.

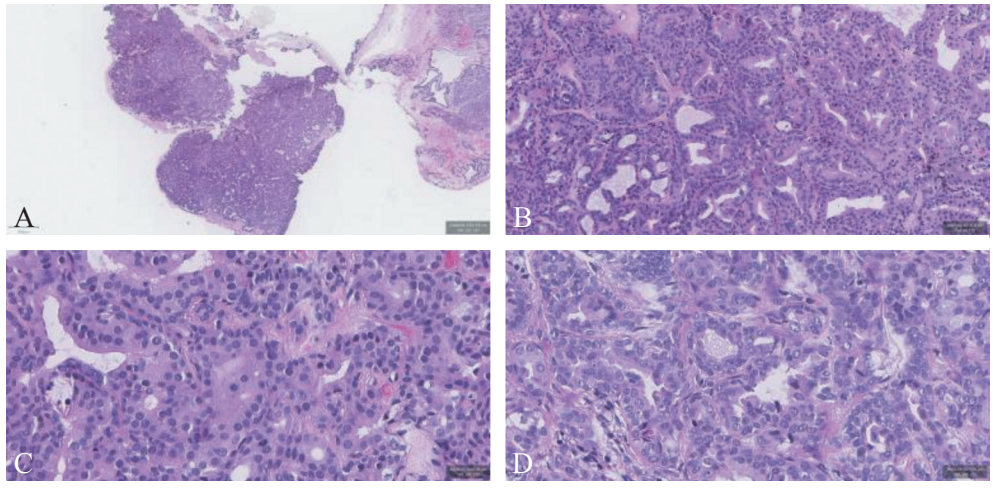

Figure 4.—Anatomopathological description: A, B) histological examination revealed an unencapsulated proliferation of glands with multifocal cribriform pattern (H&E 5× and 20×, respectively); C, D) glands were composed of an inner layer of cuboidal cells with eosinophilic cytoplasm and an outer layer of myoepithelial cells (H&E 40×).
Mitosis were completely absent.

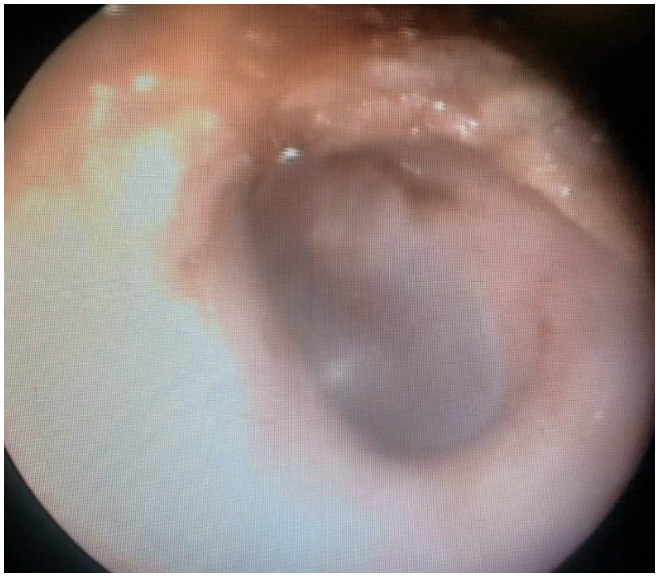

Figure 5.—Surgical result after three months.

studies, the ceruminous glands are mainly found at the cartilaginous part of the EAC.[15, 24, 28-31]

The number of cases present in the literature is certainly underestimated; much of the confusion comes from inappropriate nomenclature: for many years they were called ceruminous tumors including both benign and malignant tumors under the name ceruminoma. Currently, thanks to the new classification system this confusion has been resolved.[1, 3]

The ceruminous adenoma is a benign tumor, belonging to the class of adenomas. It is a localized tumor, characterized by the proliferation of cells histologically similar to normal ceruminous glands.[32]

No risk factors or exposure to predisposing factors are known; however, the incidence of ceruminous adenomas is around 5% of all EAC neoplasms.[3] According to some authors, this incidence could be even lower.[28, 33]

The age of presentation is highly variable, with an average age of around 50, with no sex differences. In our

review the youngest patient case described was 3 years old while the oldest was 87 years old.[22, 23]

Most ceruminous adenomas are asymptomatic or paucisymptomatic. Most of the symptoms can be due to the encumbrance caused by the mass. For this reason, we have conductive hearing loss; more rarely ear pain, otorrhea or bleeding, facial paralysis. Bleeding and pain are certainly the symptoms that most commonly make the specialist suspicious and require the exclusion of a malignant pathology.[14, 28, 33]

In only one of the treated cases was the lesion highlighted due to an ipsilateral facial spasm. however, although physical examination found the presence of a mass within the EAC on the same side as the spasm, both CT and surgical inspection excluded signs of infiltration. Therefore, the ceruminous adenoma was not responsible for the reported symptoms.[15]

On otoscopy the lesion generally appears as a soft, oval-rounded mass, generally intact, with a pink to brownish color.[12, 13, 17, 23]

In most cases, the ceruminous adenoma affects the cartilaginous tissue, only rarely does it interact with the surrounding bone.[15, 34]

Currently the symptoms are characterized by slow growth of the tumor, absence of pain; imaging (CT or MRI) demonstrating lack of involvement of the surrounding structures leads towards the diagnosis of a benign tumor.[25, 34]

Histological examination reveals the presence of apical apocrine glandular cells and myoepithelial cells at the basal level. The absence of high mitotic activity and nuclear alterations leads towards the diagnosis of a benign lesion. Immunohistochemical examination confirms the diagnosis of ceruminous adenoma. In fact, the positivity for CK 5-6, S-100 and strong reactivity for p63 protein are also found on normal glandular tissue. This confirms the benign nature of the ceruminous adenoma.[14, 17, 19, 21]

A recent study suggests the use of Glut-1, HIF-1α, PI3K and p-Ak as early markers in the immunohistochemical diagnosis of ceruminous adenoma. Glut-1 is an indicator of altered energy consumption by neoplastic tissue. HIF-1α, PI3K and p-Ak are directly involved in the cellular response mechanism to hypoxia and their activation appears to be at the basis of the mechanisms of escape from cellular apoptosis.[25]

The surgical treatment of choice is complete surgical excision characterized by the entire lesion and a portion of healthy cellular tissue. Many times, the biopsies performed turn out to be incisional. Complete excision ensures the absence of local recurrence. If the excision does not occur completely, close follow-up or revision of the surgical site is suggested. Transmittal excision is generally sufficient for small tumors; otherwise, retroauricular access is preferable. The duct is generally reconstructed with a free skin flap.[34]

Recurrences are rare although long-term follow-up is recommended. Adjuvant therapy with chemotherapy or radiotherapy is not indicated.[8, 28]

Often the biopsies performed turn out to be "incisional" rather than "excisional." For this reason, since it is not always possible to evaluate the margins of the lesion and the healthy tissue surrounding the excised neoformation, Mansour proposed classifying ceruminous adenomas as ceruminous gland tumors of uncertain malignant potential.[28]

Careful follow-up is important because, according to some authors, histological examination alone is not sufficient to guarantee that the ceruminous adenoma does not evolve into a malignant tumor.[25, 35]

The cases reported in the review demonstrated only four cases with disease recurrence after a few years. In particular, Cankar described the recurrence of a lesion at the EAC level with histological diagnosis of cylindroma.[13]

Lynde demonstrated the presence of a recurrence of ceruminous adenoma after 4 years of follow-up treated with radical mastoidectomy and radiotherapy. A second recurrence of ceruminous adenoma was discovered 6 years later. No information on subsequent treatment and follow-up is reported. Although the first operation was radical (tympanoplasty), this is a case in the literature with a recurrence 4 and 6 years after the first operation.[14]

Maranhao described the case of a patient with a previous diagnosis of ceruminous adenoma who, ten years after surgery, showed a new lesion at the EAC level. The instrumental investigations pointed towards a heterogeneous lesion with malignant characteristics. She underwent radical surgery (tympanoplasty and mastoidectomy) and subsequently radiotherapy because the histological examination showed ceruminous carcinoma. This is a rare case of malignant evolution following a previous diagnosis of ceruminous adenoma.[21]

Nishimura describes the case of a patient diagnosed with ceruminous adenoma with the presence of recurrence approximately 2 years later. Preoperative instrumental examinations showed no erosion of the surrounding structures. He underwent surgical excision, and the histological examination highlighted a ceruminous pleomorphic adenoma, a variant of the ceruminous adenoma.[27, 36]

Conclusions

Ceruminous adenoma is a benign tumor that affects the ceruminous apocrine glands of the external auditory canal. Generally asymptomatic, the diagnosis can occur incidentally. It presents as a lesion with a homogeneous, smooth appearance, without superficial erosions. The most frequent symptoms are linked to the space-occupying effect of the mass. Otorrhea or bleeding are rare. The elective instrumental investigations (CT and MRI) demonstrate the localization of the lesion without involvement of other surrounding noble structures. The treatment of choice is surgery. *En-bloc* excision with a portion of surrounding healthy tissue allows for the absence of recurrences thanks to the anatomy of the ear, the presence of surrounding bone tissue protects noble structures such as nerves. Histological examination and immunohistochemistry confirm the diagnosis. In addition to the common markers (CK 5-7; S-100), new markers have been highlighted and could be useful in explaining the growth of the ceruminous adenoma and guiding the diagnosis (Glut-1, HIF-1α, PI3K and p-Akt). Despite the benign nature of the lesion, the possibility of disease recurrence or transformation into a malignant tumor is still described. Any adjuvant therapy does not influence the natural history of the neoplasm. Complete excision and close follow-up allow control of the disease over time.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Massimo Mesolella, Pasquale Capriglione, Giovanni Motta, Rosa M. Di Crescenzo and Salvatore Allosso contributed equally to the manuscript, Massimo Mesolella and Salvatore Allosso have given substantial contributions to study conception and design, Pasquale Capriglione, Giovanni Motta and Rosa M. Di Crescenzo to data acquisition, analysis and interpretation, Massimo Mesolella, Pasquale Capriglione, Giovanni Motta, Rosa M. Di Crescenzo and Salvatore Allosso to manuscript writing, Salvatore Allosso to manuscrit critical revision. All authors read and approved the final version of the manuscript.

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Supplementary data

For supplementary materials, please see the HTML version of this article at www.minervamedica.it