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Review Article

A review of the definition, terminology and pathology of aural cholesteatoma

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Abstract
Despite a considerable amount of discussion and research in the course of many years, aural cholesteatoma has remained a matter of controversy. This review concerns only the definition, terminology and pathology of this common and severe disease.

Key words: Cholesteatoma, definition, terminology, pathology

Definition

According to Abramson *et al.* (1977) 'cholesteatoma is a three-dimensional epidermal and connective tissue structure, usually in the form of a sac and frequently conforming to the architecture of various spaces of the middle ear, attic, and mastoid. This structure has the capacity for progressive and independent growth at the expense of underlying bone and has a tendency to recur after removal'.

Cody (1977) suggests that 'the otologist defines the cholesteatoma as usually being associated with an attic defect, an extremely sclerotic mastoid process and eustachian tube dysfunction'. In Gray's opinion (1964), the simplest and most appropriate definition of cholesteatoma is 'skin in the wrong place'. McCabe *et al.* (1976) wrote the summary report on the First International Conference on Cholesteatoma, in which cholesteatoma was described not simply as skin in the wrong place, but as 'a three-dimensional epidermoid structure exhibiting independent growth, replacing middle ear mucosa, resorbing underlying bone and tending to recur after removal'.

Sadé (1982) defines the cholesteatoma histopathologically as 'an epidermoid cyst, or part of it, as in the case in retraction pockets'. Hyams (1987) considers it 'a benign keratinizing squamous cell cyst'. Vennix *et al.* (1990) believe that 'cholesteatoma can be defined as the presence of a cornifying squamous epithelium in the middle ear cavity'. Yan and Huang (1991) suggest that 'cholesteatoma is a disease that manifests as a progressive growth of skin within the middle ear'.

Cholesteatoma is not a neoplastic lesion, but it is nonetheless insidious and potentially dangerous. Histologically, it is an epidermoid cyst characterized by independent and progressive growth; it can sometimes lie dormant, but very often causes the destruction of adjacent tissue, of bone in particular, and has the tendency to recur despite extensive radical surgery.

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Terminology

The lesion in question is referred to by the ambiguous term of cholesteatoma, which is a misnomer—as Holleman (1965) pointed out—'since cholesterol is not an essential component and the lesion is actually an epidermoid cyst rather than a neoplasm'. Virchow (1855) had already emphasized that the lesion does not usually contain cholesterin when he used the term to describe an epithelial formation of embryonic origin.

The term 'cholesteatoma' was first used by the famous anatomist Johannes Müller in 1838 and he meant to describe a true neoplasm; but the lesion had already been reported by the French pathologist Cruveilhier in 1829 as 'pearly tumour' and by Pinson, an artist in the Paris School of Medicine, in 1807 and even, almost two centuries earlier, by the anatomist Jos du Verney (1683) as 'steatome', to indicate the presence of cholesteatomatous substances in and around the base of the skull. To define such a lesion arising in the brain, Cushing (1922) used the term 'epidermal cholesteatoma', whereas Critchley and Ferguson (1928), who found it in the brain and spinal cord, proposed the adjective 'epidermoid' because it was more suitable to convey the epithelial character of the growth.

In addition to the terms already mentioned, this pathological process has been labelled with still other names, creating further confusion. Some of the most common terminology includes: margaritoma (Craigie, 1828; *cf.* Virchow, 1855); pearly squamous cell carcinoma (Cornil and Ranvier, 1891); cholesteatosis (Birrell, 1958); squamous epitheliosis (Birrell, 1958); epidermosis (Tumarkin, 1958); epidermoid cholesteatoma (Friedmann, 1959); keratoma (Harris and Weiss, 1962); keratosis (McGuckin, 1963); epidermoid cyst (Ferlito, 1970) (see Table I). Schuknecht (1973) considers the term cholesteatoma 'horrible' and prefers to call the lesion 'keratoma', a term already adopted by Harris and Weiss (1962). Rüedi (1979)

TABLE I
VARIOUS TERMS DESIGNATING CHOLESTEATOMA

Terms	Author(s)	
Steatome	Du Verney	1683
Margaritoma	Craigie	*cf.* Virchow
Pearly tumour	Cruveilhier	1829
Cholesteatoma	Müller	1838
Pearly squamous carcinoma	Cornil and Ranvier	1891
Epidermal cholesteatoma	Cushing	1922
Epidermoid	Critchley and Ferguson	1928
Cholesteatosis	Young	1950
Black cholesteatosis	Birrell	1956
Squamous cholesteatosis	Birrell	1958
Squamous epitheliosis	Birrell	1958
Epidermosis	Tumarkin	1958
Epidermoid cholesteatoma	Friedmann	1959
Keratoma	Harris and Weiss	1962
Keratosis	McGuckin	1963
Epidermoid cyst	Ferlito	1970

[Modified from Friedmann I., 1978 Pathology of the ear: selected topics. In *Pathology Annual (Part 1)*, Vol. 13, pp 364–410].

stressed that in Dorland's illustrated medical dictionary the term 'keratoma' indicates a horny tumour, while Guttman's medical dictionary describes 'keratoma' as a special disease of the skin characterized by a localized thickening of the horny layer. Friedmann (1970, 1974) favours the term 'epidermoid cholesteatoma' because it is clinically descriptive and it emphasizes the role of squamous epithelium.

In their famous textbook 'Histopathology of the Ear, Nose and Throat', Eggston and Wolff (1947) wrote that 'the pathological lesion known to the otologist as 'aural cholesteatoma' is perhaps more accurately termed 'epidermoid cyst' by the general pathologists'. The term 'epidermoid cyst' accurately describes what the lesion really is. But, however susceptible it may be to criticism, the term 'cholesteatoma' is now in common usage in otological literature and is known world-wide, so attempting to change it is inadvisable.

The lesion is defined according to its location, as follows: cholesteatoma of the middle ear, aural cholesteatoma, epitympanic cholesteatoma (and, to be more precise, antero-medial epitympanic cholesteatoma, antero-lateral epitympanic cholesteatoma, postero-medial epitympanic cholesteatoma), mesotympanic cholesteatoma, pantympanic cholesteatoma, labyrinthine cholesteatoma, paralabyrinthine cholesteatoma, extramastoid cholesteatoma, cholesteatoma of the apex of the petrous bone, etc.

Such a pathological process is also defined according to the possible histogenetic mechanism from which it originates, e.g. primary cholesteatoma, true cholesteatoma, cholesteatoma verum, congenital cholesteatoma, bilateral congenital cholesteatoma, primary keratoma, primary epidermoid inclusion cyst, epithelial cyst, acquired aural cholesteatoma, primary acquired cholesteatoma, secondary acquired cholesteatoma, secondary cholesteatoma, acquired cholesteatoma, primary pseudocholesteatoma, post-natal cholesteatoma, attic retraction cholesteatoma, retraction cholesteatoma, post-traumatic cholesteatoma, invagination cholesteatoma, atelectatic cholesteatoma, ingrowth cholesteatoma, etc.

As to other than acquired cholesteatomas, several investigators (Derlacki *et al.*, 1968; Peron and Schuknecht, 1975) suggest that the term 'congenital cholesteatoma' should be adopted. Nager (1981) refers to the lesion as either epidermoid or congenital cholesteatoma, considering it as a blastomatous malformation.

Ear surgeons have introduced their own terms, such as residual cholesteatoma, recurrent cholesteatoma (retraction pocket), attic retraction cholesteatoma, recidive cholesteatoma, iatrogenic cholesteatoma, transplant cholesteatoma, implantation cholesteatoma, acquired implantation cholesteatoma, 'flap' cholesteatoma, recurring cholesteatoma, post-stapedectomy cholesteatoma, graft cholesteatoma, annulus or annulus cholesteatoma, hidden cholesteatoma, etc. In particular, the term 'recurrent cholesteatoma' refers to the development of a new cholesteatoma which arises from the skin of the tympanic membrane and the nearby meatus. It takes the form of a retraction pocket which may be seen to advance from the posterior mesotympanum into the epitympanum and antrum, in a manner similar to that of the original disease. Recurrent cholesteatoma occurs even after complete surgical removal of cholesteatoma (Smyth, 1976), whereas residual cholesteatoma is a complication arising from failure to remove all of the original cholesteatoma from the tubotympanic cleft (Smyth, 1976). The two terms are not interchangeable therefore, but in practice it is not always easy to establish with certainty whether cholesteatoma is recurrent or residual.

It is not uncommon to find still other terms, mainly adopted by clinicians, such as chronic cholesteatoma, Shrapnell's cholesteatoma, extensive cholesteatoma, destructive cholesteatoma, precholesteatoma, pocket cholesteatoma, papillary cholesteatoma, hernia-type cholesteatoma, silent cholesteatoma, latent cholesteatoma, occult cholesteatoma, etc.

A new cholesteatoma staging procedure has recently been proposed (Meyerhoff and Truelson, 1986). Congenital cholesteatoma has its nidus of trapped squamous epithelium present at birth. Primary acquired cholesteatoma is associated with a defect in the flaccid part of the tympanic membrane whereas secondary acquired cholesteatoma is associated with a defect in the tense part and tertiary cholesteatoma (a newly-introduced term) is acquired and exists behind an apparently normal tympanic membrane as the result of implantation or a previous middle ear inflammation (Meyerhoff and Truelson, 1986).

The term 'cholesteatoma of the external auditory canal' may also be found in the literature. This term has often been indiscriminantly adopted as a synonym for keratosis obturans, membranous external otitis, otitis externa crouposa, keratin granuloma, etc. (Senturia *et al.*, 1980). It is well-known that cholesteatoma of the middle ear may extend to the external auditory meatus and to the labyrinth, thus creating a fistula. 'True' cholesteatoma involving the external auditory canal has been described (Rainer, 1968; Bhide *et al.*, 1973; Smith and Falk, 1978; Piepergerdes *et al.*, 1980; Anthony and Anthony, 1982; Broekaert, 1991). Congenital cholesteatoma of the external auditory canal has also been reported (Peron and Schuknecht, 1975).

Pathological findings

Macroscopical appearance

Macroscopically, cholesteatoma appears as a roundish or oval-shaped friable mass which is whitish in colour, pultaceous in consistency, of a variable size and at times so small that its clinical detection is impossible, whereas it may sometimes reach the size of a walnut or larger, even measuring over 5 cm in diameter.

Light microscopy

It appears histologically as a benign keratinizing squamous cell cyst. The lesion is basically made up of three components, i.e. the cystic content, the matrix and the perimatrix.

The cystic content is composed of fully-differentiated anucleate keratin squames. There may be sebaceous material and some purulent and necrotic matter in the cavity. The matrix of cholesteatoma consists of keratinizing squamous epithelium lining a cyst-like structure. The cholesterol crystals are usually not part of the cholesteatoma but they may be present in the granulation tissue. The stratified squamous epithelium is characterized by the presence of intercellular bridges and a regular disposition of the various layers of cells may be found. In particular, the matrix of the cholesteatoma comprises the following:

1. The basal layer or stratum germinativum, made up of columnar epithelium composed of small cuboidal cells displaying a basophil large nucleus.
2. The malpighian or spinal layer, composed of larger cells, still relatively cylindrical in shape, which become polyhedral in the more superficial layers.
3. The granular layer in which cells become progressively flatter and contain hyperchromatic keratohyaline granules in their cytoplasm.
4. The stratum layer, which appears to be clearly hyperkeratotic and desquamating; the lamellae of keratin form the cystic content.
5. The lucid layer is often not detectable.

There are occasionally two kinds of epithelia forming the epidermoid cyst: keratinizing stratified epithelium and respiratory epithelium (Sadé *et al.*, 1982). The perimatrix or lamina propria is the peripheral part of the cholesteatoma and consists of granulation tissue or inflamed subepithelial connective tissue displaying inflammatory cells composed of lymphocytes, histiocytes, plasma cells and, less frequently, also neutrophil leucocytes. Several glandular structures may be seen, partly filled with PAS-positive material. If the cholesteatoma sac ruptures, there is spreading of the keratinous substance in the subepithelial layer and this usually causes a marked granulomatous reaction of the foreign body type. Cholesteatoma is called 'closed' when keratin is completely encysted and 'open' when keratotic debris are in free communication with the middle ear cavity and can elicit a foreign-body giant cell reaction. In continuity with the cyst, neither cutaneous adnexa or their remnants nor dermal papillae are ever seen (Ferlito, 1970; 1974a,b). Osteoclasts are frequently found at the interface between the cholesteatoma matrix and the underlying bone.

All cholesteatomas exhibit the same morphological aspect, regardless of their mechanism of formation, but there is a substantially greater thickness of the matrix in the acquired variety than in the congenital variety (Michaels, 1988, 1990). The matrix of acquired cholesteatoma is usually composed of approximately 15 layers of cells whereas that of congenital cholesteatoma comprises only about five layers.

Cholesteatoma causes severe bone destruction by a mechanism which does not appear to be connected with pressure necrosis, as claimed by some investigators (Rüedi, 1958, 1979; Tumarkin, 1958). Friedmann (1981) is of the opinion that bone erosion is due to the inflammatory granulation tissue (and its components) and that various proteolytic enzymes play an important role. The escape of the contents from the cholesteatoma sac into the subepithelial layer is considered an important factor in bone destruction (Kaneko *et al.*, 1980). Osteoclast bone resorption has been observed in chronic otitis media with and without cholesteatoma.

Immunocytochemistry

Recent studies have indicated that cytokeratins may serve as excellent markers to differentiate cholesteatomas of epidermal origin from those of non-epidermal origin (Vennix *et al.*, 1990) though the cytokeratins present in the cholesteatomas are usually similar to those of the meatal epidermis (Chao and Huang, 1989; van Blitterswijk *et al.*, 1989; Lee *et al.*, 1991; Broekaert *et al.*, 1992). Langerhans cells show reactivity for S-100 protein (Takahashi and Nakano, 1989).

Electron microscopy

The structure of cholesteatoma was investigated by electron microscopy by several investigators (Ikeda, 1968; Bodelet and Wayoff, 1972; Lim and Saunders, 1972; Brémond *et al.*, 1975; Brémond and Magnan, 1977; Lim *et al.*, 1977; Mann *et al.*, 1981; Gantz, 1984; Visser *et al.*, 1987).

The ultrastructural features of the different cell layers were no different from those of normal epidermis. There are keratinocytes both in the skin and in the epithelial layers of cholesteatoma. Ultrastructural investigations have revealed two particular types of cell in human cholesteatoma, i.e. Langerhans cells and Merkel cells. The former are located within the prickle-cell layer, between keratinocytes, the latter within the germinative layer. They are connected to neighbouring keratinocytes by desmosomes (Brémond *et al.*, 1975). These two types of cell were first described in the skin. They are believed to be mesenchy-

TABLE II
FEATURES DIFFERENTIATING CHOLESTEATOMA FROM CHOLESTEROL GRANULOMA

Cholesteatoma	Cholesterol granuloma
Composed of a perimatrix (fibrous tissue), a matrix (stratified squamous epithelium) and always containing horny lamellae in the cystic lumen	Composed of fibrous tissue in which cholesterol crystals may be seen, surrounded by numerous inflammatory cells and by several giant cells of the foreign body type
Morphologically an epidermoid cyst	Morphologically, a reactive foreign body granuloma
Basically an 'epithelial' lesion	A 'stromal' lesion
May not be connected with a chronic inflammatory process	Almost always represents a focal response to chronic middle ear infection
CT	
Margins: sharp, smooth	Sharp, smooth
Density: isodense to cerebrospinal fluid	Isodense to brain
Enhancement: no	No
MRI	
T_1-weighted signal intensity: low	High
T_2-weighted signal intensity: high	High
Associated with erosion or displacement of the ossicles	May be associated with adjacent erosion of ossicles and bone

mal in origin and they differ from the foreign body giant cell by the arcuate arrangement of their nuclei. Both Langerhans and Merkel cells are of unknown origin and function (Laurence, 1977). Lim *et al.* (1977) have also shown evidence of a paucity of melanocytes in the cholesteatoma matrix. Langerhans cells have also been found in experimentally-induced squamous metaplasia of the trachea and bladder. Perhaps Langerhans cells play a role in the pathophysiology of cholesteatoma through interaction with T-lymphocytes (Gantz, 1984).

Scanning electron microscopy

These studies have revealed the presence of corneocytes in the shape of a hexagonal disc, arranged in regular columns, with each column surrounded by six others (Youngs and Rowles, 1990). Langerhans cells have also been found (Paludetti *et al.*, 1989).

Differential diagnosis

Cholesteatoma is often mistaken by clinicians and pathologists for cholesterol granuloma. Friedmann (1957, 1970) pointed out that cholesteatoma and cholesterol granuloma should be considered as two different pathological entities exhibiting distinct histopathological features. Cholesteatoma is an epidermoid cyst (Eggston and Wollf, 1947; Friedmann, 1957a, 1974; Abramson, 1969; Ferlito, 1970, 1973a,b, 1974a,b, 1975, 1979; Sadé, 1982), whereas cholesterol granuloma is a lesion characterized by a granulomatous structure and formed by large numbers of cholesterol crystals surrounded by foreign body giant cells and embedded in fibrous granulation tissue (Friedmann, 1959).

TABLE III

Clinical diagnosis	Histopathology
Cholesteatoma	Cholesteatoma confirmed
Cholesteatoma	Unconfirmed
Cholesteatoma	Keratinized squamous epithelium
No clinical evidence	Cholesteatoma present
Cholesteatoma	Chronic otitis media and cholesterol granuloma
Chronic otitis media	Squamous epithelium present (non-keratinizing)

(Modified from Friedmann I., 1977. *Cholesteatoma. First International Conference.* Aesculapius, Birmingham, pp 10–22).

In spite of the fact that several studies have been published stressing the difference between the two pathological processes, there is still confusion in the literature. Mawson (1974) claims (wrongly, in my opinion) that: 'Histologically, cholesteatomas are of two types, epidermoid cholesteatoma and cholesterol granuloma'. In Anderson's pathology text (1971), Wilkes labels as cholesteatoma of the middle ear a lesion which is clearly cholesterol granuloma. In a paper entitled 'Black cellular cholesteatosis in children', Birrell (1956) includes some illustrations of cholesterol granuloma misinterpreted as cholesteatoma.

The CT scan appearance of cholesterol granulomas may be indistinguishable from that of cholesteatomas, but the MR image of cholesterol granuloma is characteristically one of high signal intensity on both T_1- and T_2-weighted images because of the paramagnetic effects of protein content and cholesterin (Griffin *et al.*, 1987; Martin *et al.*, 1989; Goldofsky *et al.*, 1991). Cholesteatomas have been found iso-intense or hypo-intense on T_1-weighted images and of high signal intensity on T_2-weighted images (Kerstetter and Dolan, 1991).

For the sake of clarity, Table II illustrates the differences between cholesteatoma and cholesterol granuloma. Cholesteatoma should also be distinguished from squamous metaplasia and keratinizing squamous metaplasia. Sheehy erroneously wrote in 1978 'residual cholesteatoma is the term we have used to describe squamous epithelium not removed from the tubotympanic cleft in cholesteatoma surgery'. This statement clearly suggests that the surgeon identified squamous epithelium with cholesteatoma, but this is a mistake. Schuknecht (1973) rightly says: 'large areas of the middle ear contain keratinizing surface epithelium, which should be called areas of epidermization. They are not cholesteatomas in my opinion'.

Cholesteatoma should also be differentiated from squamous cell carcinoma. Despite the associated inflammatory changes, the epithelial component of a cholesteatoma does not usually show significant dysplasia (Barnes and Peel, 1990). The clinical diagnosis does not always correspond to the pathological aspects of the lesion (see Table III).

Cholesteatoma associated with other diseases

Cholesteatoma is often associated with chronic otitis media, but it may also be associated with tympanosclerosis (Ferlito, 1979, 1982), with cholesterol granuloma, with atelectasis of the ear (Sadé, 1979) and with cleft palate (Dominguez and Harker, 1988).

Cholesteatoma may also occur in association with ear malformation (Goufas, 1932; David, 1934; Gignaux, 1953; Ombrédanne and Porte, 1962; Peron and Schuknecht, 1975; Huang, 1986; Mills and Graham, 1986). Jahrsdoerfer (1978) reported that in over 1600 operations for major and minor atresia of the ear, Ombrédanne (1976) had encountered 72 cases of primary cholesteatoma, which means a percentage of 4.5 per cent.

Bilateral congenital cholesteatomas of the middle ear associated with salivary choristomata and other anomalies of the middle and inner ears have also been reported (Peron and Schuknecht, 1975) and an osteoma of the middle ear associated with congenital cholesteatoma has been described (Yamasoba *et al.*, 1990).

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