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RESEARCH ARTICLE

ETIOPATHOLOGY OF ACQUIRED CHOLESTEATOMA

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ABSTRACT

The etiopathology of acquired cholesteatoma has undergone numerous changes over the past 150 years. However, certain facts stand out with clarity. The presence of cytokeratins in acquired cholesteatoma, which are akin to those found in the tympanic membrane and external auditory canal, shows that these are probably the site of origin of acquired cholesteatoma. The cholesteatoma sac also shows its greatest growth at its tympanic membrane attachment into the middle ear. Implantations of squamous epithelium due to trauma or surgery could be another originating factor. The basic pathology is the formation of papillary cones from the tympanic membrane or external auditory canal, which progress from microcholesteatoma to frank cholesteatoma with keratin collections. There is an altered matrix metalloproteinase pathway. Tumor necrosis factor activation with altered wound healing process contributes to the collateral destruction of bone. Trisomy and aneuploidy of chromosome 8 predispose to cholesteatoma formation in affected individuals. In this article, we present the etiopathology of acquired cholesteatoma as it stands today.

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INTRODUCTION

Since Virchow's first publication on cholesteatoma in 1855, the theories of etiology and spread of acquired cholesteatoma have undergone extensive changes. Different postulates have jockeyed for position at various times and diverse causative factors have been recognized and then discarded. Some facts have been borne out by research. Retraction pockets, external canal keratosis and mucocutaneous junctions at the edges of tympanic membrane perforations are recognized as "precholesteatomatous" conditions. Keratin retention is the hallmark of cholesteatoma and infection is an important factor for propagation and spread. Chromosomes 7, 8 and 17 are the key in determining individual susceptibility to cholesteatoma formation. The tympanic membrane is possibly the anatomical area from where the cholesteatoma arises in the form of papillary cones which then grow inward. The metaplasia theory is now without support. Matrix-permatrix reactions cause the cholesteatoma to invade the surrounding middle ear structures and the mastoid bone.

DISCUSSION

Cholesteatoma, named by Muller in 1838, remains as much an enigma today. It is recognized to be of two broad classes: congenital and acquired. The former is easier to comprehend in terms of origin and progression, being a result of trapped cell nests within the petrous sutures. It is the latter which confounds analysis; this unfortunately translates into difficulties of treatment because mechanisms of pathology are ill understood. Tos divided cholesteatoma into two main classes: attic cholesteatoma and pars tensa cholesteatoma.(2) The latter was further divided into marginal and central disease. Another type of cholesteatoma behind an intact drum was added by Mills and Padgham.(3) These different divisions do not affect the basic cellular mechanism. Inflammation in the tympanic membrane and middle ear are singularly important in the pathophysiology of cholesteatoma, especially in recurrent cases and in spread of disease to the labyrinth, facial nerve and intracranial space (1.4-8) There is obviously an imbalance in fibroblast collagen activity and growth factor βactivity. The tympanic membrane is a triple-layered structure at the end of a cul-de-sac, where it is dependent on "migration" of its overlying epidermal cells for cleansing. Retraction pockets hamper the process. Accumulation of keratin in retraction pockets may transform them into cholesteatoma. Improper Eustachian tube function with consequent negative middle ear pressure and decreased mastoid pneumatization are the etiological factors for cholesteatoma. Ongoing inflammation hastens the pathology" (1,6,9-13). Aneusomy of chromosomes (7, 8, 17) may harbor the genetic cause for predisposition of some ears to cholesteatoma formation.(14) Chronic inflammation in the middle ear creates hypoxic conditions with

decreased ventilation resulting in tympanic membrane retractions. Growth factor ß and vascular occlusion are known factors in the pathogenesis of cholesteatoma and are the end result of middle ear hypoxia.(15-18) Here, it would be worthwhile to peruse the anatomy of a cholesteatoma sac. Containing keratin within, it has a sac cover of matrix (keratinized squamous epithelium) and a perimatrix (subepithelial connective tissue with cuboidal epithelial layer). There is a distinct growth pattern of papillary cones and keratin deposit (lacunae) which later fuse to form cysts.(1 What results is a keratin sac or cholesteatoma. Inflammation and infection are added, which are the important factors for further propagation of this disease. Altered matrix and perimatrix behavior patterns are the basic pathological processes. Angiogenesis or the lack of it in the disease area would further impact the disease. Persaud *et al*. have reviewed the theories of acquired cholesteatoma.(21)

Metaplasia theory: The metaplasia theory put forth by Sade *et al*. (22) has not been borne out by the ultrastructural or immune cytochemical studies. (23,24) However, cholesteatoma epithelium is seen to possess the same cytokeratins and locomotor properties as the external auditory canal and tympanic membrane.(25,26)

Immigration theory: Epithelium from the edge of tympanic membrane perforation has been shown to migrate into the middle ear. (27-29)

Basal hyperplasia theory: Ruedi *et al*.(30) suggested in the presence of inflammation, basal cell activity increases and the proliferation of cells causes them to break past the intact tympanic membrane into the middle ear.

Iatrogenic or implantation theory: Wullstein and Mckennan and Cole(32) showed cholesteatoma developing from skin accidentally implanted into the middle ear as a result of surgery. A similar process could be considered for post-traumatic cases.

Retraction pocket theory: Eustachian tube malfunction causes the tympanic membrane to retract.(33,34) This results in weakening of the fibrous component of the drum, leading to hyperplastic epidermal growths into the middle ear.(35,36) Ongoing infection could then result in the development of cholesteatoma. Louw has elegantly enumerated the pathology of precholesteatoma and cholesteatoma.(37) Mucocutaneous junctions at the edges of tympanic membrane perforations are definitive precholesteatoma conditions.

The perforation may be post traumatic, post surgery or post inflammatory. Keratinizing squamous epithelial cells produce papillary cones which protrude into the middle ear cavity.(19) Infection transforms the condition into cholesteatoma. (15,38) Retraction pockets also show focal growth of keratinizing squamous epithelium, which progresses from a precholesteatoma to frank cholesteatoma.(19) Focal areas of an intact tympanic membrane may show a similar hyperplastic growth of keratinizing squamous epithelium to develop cholesteatoma behind an intact drum.(39) Trauma and previous ear surgery may trap epithelial cells in the middle ear, which can progress to cholesteatoma.(37) Adhesive otitis media can drape the tympanic membrane over the ossicles and promontory and lead to cholesteatoma.(6,40) Ensuing or coexisting infection would be essential in further propagation of the disease.

The external ear may also be the seat of a cholesteatoma. Infection and keratin debris here stimulate local epidermal hyperplasia.(19,38,411 Squamous epithelial perforation leads to formation of keratotic masses which invade the tympanic cavity. Here too, papillary cone formation is the main feature. The migration and metaplasia theories are under question today. Sudoff and Toss found no clinical evidence of these (19). At the most, migration may represent a precholesteatoma condition.(42) Louw had traced the progression of epidermal hyperplasia to cholesteatoma.(37) Epidermal papillary cones form, which under the influence of inflammatory mediators and collagenases, undergo central desquamation (lacunae) to form microcholesteatoma. The latter expand to form larger keratin cysts. There is ongoing matrix and perimatrix interaction and derailment of matrix metalloproteinase system. This is what causes the cholesteatoma to invade the middle ear and mastoid. Tumor necrosis factor and enzymes present in the cholesteatoma cause erosion of the surrounding bone.

Huisman *et al*. concluded that cholesteatoma behaves as a chronic wound healing process.(43) They showed consistence relationships between transforming growth factor- ß (TGF-ß), nuclear pSmad (phosphorylated Smad) 2 and Smad7. TGF-ß affects proliferation and migration of different cell types and controls inflammatory processes and apoptosis. In their studies, cholesteatoma stained positive for TGF-ß, nuclear pSmad2 and Smad7. They also showed a TGF-ß bioactivation increase in cholesteatoma epithelium. Cholesteatoma keratinocytes showed spindle shapes, migration, augmented extracellular signal regulated kinase (ERK)1⁄2 mitogen-activited protein kinase (MAPK) signaling and phosphatidylinositol 3-kinase (AKT/protein kinase B) activation. The authors concluded. that cholesteatoma would therefore appear to be an altered wound healing mechanism and an imbalance of the immune response. Angiogenesis and bone erosion have also been explained on similar terms. Trisomy and aneuploidy of chromosome 8 are important in the etiopathogenesis of cholesteatoma. Homoe *et al*., in their report on family clustering of acquired middle ear cholesteatoma, indicate the importance of hereditary factors.(44) Phenotypical features and genetic molecular factors with concomitant infection could be the key factors for acquired cholesteatoma.

The role of biofilms has been studied by Cole *et al*.(45) and Macassey *et al*.(46) Gram-positive, gram-negative bacteria and Pseudomonas aeruginosa produce biofilms which cause antibiotic resistance in cholesteatomatous ears. Tumors have altered apoptotic pathways and lipid-driven mitogenetic mechanism, which are essential for their growth.(15,47) A similar mechanism could be involved in the etiopathogenesis of cholesteatoma and the hyperplasia of squamous epithelium seen therein.

CONCLUSION

Despite the confusion surrounding the etiopathogenesis of acquired cholesteatoma, certain points stand out with clarity. Precholesteatoma conditions exist, e.g. retraction pockets and mucocutaneous junctions at the edges of tympanic membrane perforations. Eustachian tube dysfunction with resultant negative middle ear pressure and decreased mastoid pneumatization are predisposing factors for the development of cholesteatoma. Cholesteatoma seems to arise from the epithelial cells of the tympanic membrane and external

auditory canal. This is borne out by the presence of cytokeratins in the cholesteatoma which resemble the skin of the external auditory canal. The greatest growth area of the cholesteatoma sac is at the neck which is attached to the tympanic membrane. Cholesteatoma arises either from the epithelial hyperplasia of the tympanic membrane, papillary ingrowth from the tympanic membrane (cones), epithelial hyperplasia at the mucocutaneous junction of the tensa perforation or by implantation of squamous epithelium in the middle ear (by surgery or trauma). The metaplasia theory seems to be losing support. Infection is important in further progression of disease due to matrix and perimatrix reactions and an altered wound healing response. Altered apoptotic pathways and mitogenic mechanisms may be responsible for cholesteatoma growth and central necrosis. Cholesteatoma is a potentially dangerous condition due to the vital structures lying in close relation to the mastoid and middle ear. Only when the etiopathogenesis is truly understood, the treatment will be much more effective and recurrence rate can be controlled. Genetic variation may explain the predilection of some individuals to develop cholesteatoma and its baffling recurrence despite good surgical methods.

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