XI IAPO Manual of Pediatric Otorhinolaryngology

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Introduction

Cholesteatomas are benign growths in the middle ear and mastoid cavity that are characterized by migration of keratinized, hyperproliferative, squamous epithelium within a fibrous stoma. There exists a chronic inflammatory state that results in destruction of local anatomic structures including ossicular and bony erosion. Potential complications of advanced disease include otomastoiditis, facial nerve injury, perilymphatic fistula, intracranial spread of infections causing meningitis or abscess, and lateral sinus thrombophlebitis. The most common presenting symptoms are otalgia, otorrhea, and hearing loss. Conductive hearing loss is one of the early symptoms of cholesteatoma as it affects ossicular transmission of sound. Degree of conductive loss is not always reflective of severity of disease given variable growth patterns of cholesteatoma as well as the ability of cholesteatoma to conduct sound. Treatment for cholesteatoma is surgery, and several procedures are often needed. The main goal of surgery is to eliminate the pathology; hearing restoration in patients with advanced disease affecting the conduction apparatus in the middle ear is a secondary consideration. Hearing outcomes are variable, with postoperative air-bone gaps falling within the normal range in 53% to 77% of patients. The pathophysiology of cholesteatomas is complex, and varies in congenital versus acquired cholesteatomas. There are additional differences that have been identified in the growth patterns and biologic activity of cholesteatomas between adult and pediatric cholesteatoma patients. These differences are reflected in the more aggressive disease patterns seen in pediatric patients, which has clinical and treatment implications.

Pathophysiology

There are multiple proposed theories regarding the pathophysiology of cholesteatomas; the true etiology is likely multifactorial. Cholesteatomas are benign growths, so while locally aggressive, they are not neoplasms that can metastasize or demonstrate genetic instability. Cholesteatoma formation is characterized by both a molecular dysregulation as well as an appropriate surrounding environment including pro-inflammatory cytokines, growth factors, and bacterial toxins. Histologically, cholesteatomas typically appear as keratinized epithelium with a highly vascularized and inflammatory matrix including a large amount of mast cells, polymorphonuclear leukocytes, and granulation tissue.

Cholesteatomas are comprised of activated keratinocytes as seen in wound healing and other pathologic conditions. These cells are migratory and proliferative, and have become activated in response to growth factors, chemokines, and local cytokines. Transcription factors become activated via responding intracellular signaling pathways; these transcription factors regulate expression of keratin
genes that are associated with activated keratinocytes. Cholesteatoma cells have been shown to express proliferation cell nuclear antigens across all layers; normal ear canal skin obtained from the same patient expresses these antigens only in the basal layer. While there is an increase in proliferation in cholesteatomas, there is also an increase in apoptosis compared to control cells from canal skin, which is one factor that distinguishes cholesteatomas from malignant tumors.

Cholesteatomas can be classified as congenital or acquired. Congenital cholesteatomas are far less common than acquired cholesteatomas, and have a different pathophysiological origin. They occur behind an intact tympanic membrane usually in the anterior superior mesotympanum, originating as squamous epithelial rests. Criteria to define congenital cholesteatomas were outlined by Derlacki and Clemis; their definition includes the presence of an intact tympanic membrane in a patient without a history of otitis media. Etiologically these cholesteatomas are derived from persistent embryological remnants of epithelium in the middle ear. Based on a study of fetal temporal bones, Micheals described the epidermoid formation, which pulls the leading edge of the developing endodermal first pharyngeal pouch. This formation regresses by 33 weeks of gestation; when it fails to do so it leads to the development of a congenital cholesteatoma.

There are several studies suggesting a genetic component to the development of congenital cholesteatomas. One study of cochlear implant patients found that the incidence of congenital cholesteatoma is higher in patients with inherited forms of sensorineural hearing loss (SNHL) compared to the rest of the population. Along those lines, another study looked at the expression of the classic SNHL gene GJB2 in patients with congenital cholesteatoma. Connexin 26, a gap junction protein encoded by the GJB2 gene, is expressed in cholesteatoma and has been also shown to be important in epidermal homeostasis. GJB2 mutant variations were more prevalent in pediatric patients with cholesteatoma compared to the rest of the population, suggesting the possibility aberrant genetic connexin 26 expression as contributing to the multifactorial pathogenesis of this disease process.

The pathogenesis of acquired cholesteatomas is more complex. Theories are based on the structure and function of the tympanic membrane, a three layer structure composed of an outer epithelial layer derived from ectoderm, a middle fibrous later derived from mesoderm, and an inner mucosal layer derived from endoderm. The outer layer is composed of keratinizing epithelium that is chronically exposed to environmental and infectious insults. As part of its defensive function, the outer epithelial cells migrate outward and laterally to clean and protect the tympanic membrane and external auditory canal. The pathology of acquired cholesteatoma involves tympanic membrane epithelium migrating inward. This invagination of keratinized squamous epithelium occurs through a retraction pocket, usually from chronic eustachian tube dysfunction causing negative pressure in the middle ear. This retraction pocket theory was proposed by Tos in 1988 and remains the most popular theory describing the pathogenesis of acquired cholesteatomas. The retraction pocket occurs in the pars flaccida, which is the weakest area of the tympanic membrane as it only has two layers. Interestingly, the epithelial layer
of the pars flaccida is thicker and more proliferative than the rest of the tympanic membrane\textsuperscript{11}. As cholesteatoma forms within the deepest pocket of the retraction \textsuperscript{12}, the neck becomes obstructed by debris; meanwhile the epithelium continues to proliferate while migration remains blocked.

**Pediatric Cholesteatomas**

Despite congenital cholesteatomas being unique to the pediatric population, the majority of pediatric cholesteatomas, around 70\%, are acquired\textsuperscript{13}. Multiple authors have demonstrated that rates of recidivism in the pediatric cholesteatoma population are two to three times higher than compared to the adult cholesteatoma population\textsuperscript{14-16}. Some controversy exists as to whether pediatric cholesteatomas are inherently more aggressive than adult cholesteatomas; some have proposed that this high rate of recidivism is because surgeons are less aggressive with their pediatric patients. Indeed surgeons are less likely to utilize wall-down procedures in pediatric patients compared to adults\textsuperscript{17-20}. Some consider the prospect of lifelong dry-ear precautions and mastoid bowl maintenance as significant in altering surgical decisions to a less “radical” procedure.

However, there do appear to be biological differences between pediatric and adult cholesteatomas. Palva\textsuperscript{21} described that pediatric cholesteatoma have more extensive growth patterns than their adult counterparts. Reasons for this finding remain to be clearly elucidated. It has been suggested that pediatric patients tend to have less temporal bone sclerosis due to a shorter time progression to disease, and that better aerated mastoids allow easier access and faster spread of cholesteatoma to the deeper air cells within the temporal bone. Another theory proposes that the increased incidence of infectious otitis media in children may cause local stimulation of cholesteatoma to become more aggressive\textsuperscript{22}. Finally, it has been suggested that the growth factors that are at increased levels in the pediatric population may stimulate cholesteatoma cells to proliferate.

Regardless of the etiology of this more aggressive growth pattern of pediatric cholesteatomas, biological differences can be identified between adult and pediatric cholesteatomas. An elevated proliferation rate of cholesteatoma cells in pediatric patients has been demonstrated, with increased levels of MIB-1, a nuclear antigen expressed by cells active in the cell cycle\textsuperscript{23}. A study of 60 pediatric acquired cholesteatomas compared to 60 adult cholesteatomas showed that the pediatric specimens were characterized by thicker epithelial matrices, they expressed higher levels of matrix metalloproteinases, and they exhibited an exaggerated inflammatory profile\textsuperscript{24}. All of these findings represent factors reflective of an inherently more aggressive biological phenotype in pediatric cholesteatoma.

Clinically the aggressive nature of pediatric cholesteatoma is reflected in the higher rates of recidivism compared to adult cholesteatoma patients (Table 1). The percentage of residual disease in adults in these studies ranged from 15\% to 32\% \textsuperscript{14-16}. The percentage of residual disease in pediatric patients ranged from 21\% to 51\% \textsuperscript{2,14-16,25-27}.

In all studies that compared adult and pediatric outcomes with the same surgeon, the rate of residual disease was higher in their pediatric patients\textsuperscript{14-16}. Congenital cholesteatomas have a particularly high rate of recurrence\textsuperscript{13}; in the
### Table 1. Residual and recurrent lesions in children and adults

<table>
<thead>
<tr>
<th>Series</th>
<th>Residual (%)</th>
<th>Recurrences (%)</th>
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<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Adults</td>
</tr>
<tr>
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<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Charachon (1984)</td>
<td>51</td>
<td>23</td>
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<td>Sheehy (1985)</td>
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<td>19</td>
</tr>
<tr>
<td>Schuring (1990)</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>Iino (1998)</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Lazard (2002)</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Yung (2007)</td>
<td>21</td>
<td>-</td>
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<tr>
<td>McRacken (2011)</td>
<td>23</td>
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Pediatric population they are significantly associated with higher rates of recurrence compared to acquired cholesteatomas. One theory related to their unique pathogenesis postulates that this is because of their significant submucosal element. Additional factors include their tendency to grow medially towards the stapes and oval window, as well as the frequent delay in their diagnosis.

Several recent studies have attempted to identify clinical risk factors for residual disease to help define at-risk populations that warrant a more aggressive surgery. In looking at congenital cholesteatomas, Stapleton et al found that ossicular erosion and medial disease behind the malleus or incus were significantly associated with residual disease. Another study of patients with congenital cholesteatomas demonstrated that atticotomy at time of primary surgery as well as incus erosion were significant in predicting residual disease. In acquired cholesteatomas, sinus tympani disease and incus erosion have been found to be significantly associated with residual disease.

**Conclusion**

Cholesteatoma is a squamous hyperproliferation condition within the middle ear that occurs as a reaction to inflammatory dysregulation. Internal second messenger systems lead to increased invasiveness and proliferation, causing this dysregulation. The presence of chronic infection in this setting is likely to act as a trigger for this cascade. The proliferating cholesteatoma thrives within a cycle of inflammation and infection. There have been biological differences identified between pediatric cholesteatomas and adult cholesteatomas. While the differences still need further characterization, these biological variances are reflected in what is likely a more aggressive disease process in pediatric patients. This is an important consideration for physicians managing these patients, both in terms of surgical decision making as well as counseling patient expectations.

**References**