Cholesteatoma (Part I)  
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Definition –

- Cholesteatoma is a three dimensional epidermal and connective tissue structure, usually in the form of a sac and frequently conforming to the architecture of the 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, displacing or replacing the middle ear mucosa, and has a tendency to recur after removal.

- Abramson

(Cholesteatoma – First International Conference, Birmingham, 1977)

Theories of cholesteatoma

- Middle ear cholesteatoma occurs as two principle different entities
  - Congenital
  - Acquired
    - Primary acquired or attic retraction pocket cholesteatoma
    - Secondary acquired cholesteatoma
      - Occurs secondary to epithelial migration into the middle ear at the site of a tympanic membrane perforation or iatrogenically implanted during an otologic procedure

- Primary acquired cholesteatoma
  - Four predominant theories
    - Invagination (whitmack’s)
    - Basal cell hyperplasia or papillary ingrowth (Reudi)
    - Metaplasia (Sade)
    - Epithelial invasion
  - The invagination theory is currently regarded as one of the primary mechanism of the formation of primary acquired attic cholesteatoma
Dysfunctional eustachian tube

Impaired ventilation in middle ear

Structural weakening of the tympanic membrane

Development of retraction pockets

Pars flaccida, having the weaker structural support, is the most common site of formation of a retraction pocket

Progressive retraction --> geometrical changes due to narrowing of anatomic passages --> impairment of epithelial migration and cleaning of keratin debris

Pocket deepens and insinuates between mucosal folds and crevices --> becomes non-self cleaning --> accumulation of keratin debris
Bacterial proliferation and super-infection of accumulated debris

- amorphous polysaccharide matrix by bacteria --> biofilm

- cytokine mediated inflammatory response --> epithelial proliferation

- local release of collagenases

- breaks in the basement membrane --> formation of epithelial cones

- grow toward stroma (papillary ingrowth theory)

- microcholesteatoma (hallmark of precholesteatomatous stage)
microcones expand and fuse together

attic cholesteatoma

expand by invading into surrounding middle ear soft tissue structures and bone

↑ calgranulin A, calgranulin B, psoriasin, thymosin beta-10 --> involved in cell proliferation

↑ cathepsin C, cathepsin D, cathepsin H, and matrix metalloproteinase 9 (MMP-9) --> involved in cell invasion

↑Cathepsin B, IL 1 & 8, TNF α, nitric oxide --> ↑ osteoclastic activity & osteolysis

↑ TNF, Caspase-8 activation --> involved in ↑ apoptosis --> increased cell death --> production of larger amount of keratin debris --> further expansion and keratin accumulation
• Some other related factors
  o ↑ cytokeratin → Indicates ↑ epithelial migration & spread of cholesteatoma
  o ↑P53 → attempt by body to down regulate growth
  o Young age → ↑ aggressiveness (due to higher proliferation index) e.g. children
  o ↑calgranulin A, calgranulin B, psoriasin, thymosin beta -10 → involved in cell proliferation
  o ↑cathepsin C, cathepsin D, cathepsin H, and matrix metalloproteinase 9 (MMP-9) → involved in cell invasion
  o Cathepsin B involved in osteolysis
  o Caspase- 8 activation, ↑TNF → involved in ↑apoptosis → increased keratinocyte proliferation is coupled with an increased cell death resulting in the production of larger amount of keratin debris → responsible for the expansion and keratin accumulation seen in cholesteatoma

Secondary acquired cholesteatoma

• Theories
  o Migration of tympanic membrane epidermis into the middle ear at the site of a marginal perforation (Bezold)
  o Implantation of viable keratinocytes into the middle ear cleft
    ▪ During a blast injury to the tympanic membrane leaving keratinocytes behind a healed perforation
    ▪ At site of a temporal bone fracture
    ▪ Result of an iatrogenic introduction of these cells
      • Stapedectomy,
      • Tympanoplasty
      • Grommet insertion
        o Increased incidence in
          ▪ Age <5 yrs
          ▪ Goodle T-tubes
          ▪ Frequent reinsertions
          ▪ Duration of placement exceeding 12 months
          ▪ Ears with history of frequent postoperative otorrhea
Possible mechanisms

- Prosthesis extrusion independent of eustachian tube dysfunction
- Inadvertent implantation of keratinocytes with the oval window fat graft
- Malpositioned inverted tympanomeatal flap
- Migration at site of a marginal tympanic membrane perforation

- Middle ear exploration