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Perspective

A Spotlight on Recent Developments in Diagnosis and Treatment of Cholesteatoma

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Introduction

In 1838, when Johannes Müller first described Cholesteatoma, he thought that it was a tumour of the fatty tissue, (Latin: steat=fat). The reported annual incidence of Cholesteatoma worldwide is around 10 per 100,000. There have been reports of association between cholesteatoma and pediatric progressive sensorineural hearing loss [1]. Cholesteatoma ears show reduced microbial diversity with predominance gram positive cocci *Staphylococcus aureus.* Staph aureus cocci are associated with a progressive form of Cholesteatoma [2].

Syndromic cholesteatoma

Langerhans cell histiocytosis (LCH), Turner Syndrome, Sotos syndrome, Treacher Collins Syndrome, Down Syndrome, and Focal Dermal Hypoplasia are few syndromes that have been described in literature that are associated with a higher risk of developing Cholesteatoma [3]. Up to 6% of Cleft palate children turn out with a Cholesteatoma owing to defective middle ear ventilation, due to defective development of Tensor Tympani muscle [4].

Unclassifiable type which is a cholesteatoma is an enigmatic type of Cholesteatoma in addition to Congenital and Acquired (Primary and Secondary) whose category cannot be definitely determined [5]. Congenital Cholesteatoma are thought to grow at rate of 1mm year but growth maybe exponential or even static in few cases [6]. Lower serum Vitamin D is found in association with Cholesteatoma [6].

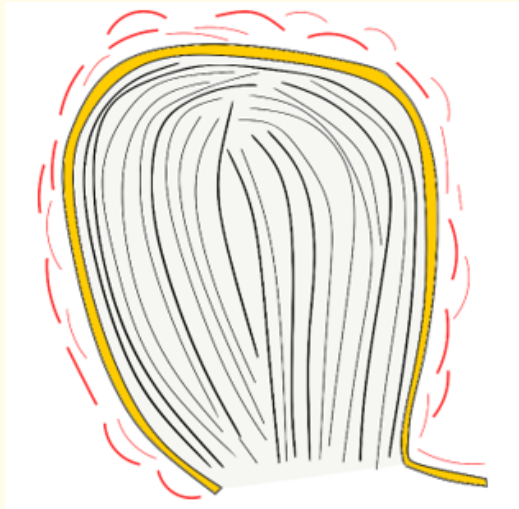

Figure 1: Schematic illustration of a Cholesteatoma, that is sac like structure containing desquamated squamous epithelial and keratin debris resting on a fibrovascular stroma. Original illustration by author himself.

Developments in imaging cholesteatoma

High-resolution computed tomography (HRCT) scans which can be used to compute the Hounsfield unit (HU) index parameter. HU measured in Scutum, Malleus and Incus was statistically lower in Cholesteatoma patients indicating occult decalcification [7].

Magnetic Resonance Imaging (MRI) Scan is a valuable new addition in visualization of Cholesteatoma distinguished by a

bright signal on T2 weighed scans and dark on T1 weighed scans. Post Gadolinium contrast Cholesteatoma does not enhance while the surrounding matrix and inflammation start to enhance 30 to 45 minutes post injection [8].

Diffusion weighted imaging MRI (DWI-MRI) protocol shows small keratin debris. There is limited water diffusion as swelling contains lipid-rich Keratin. DWI can identify recurrent Cholesteatoma and labyrinthine bone erosion especially overlying the Semicircular canals. Non-Echo Planar Imaging (non-EPI) using Diffusion-Weighted Magnetic Resonance Imaging (MRI) is highly sensitive and specific protocol for diagnosis of Cholesteatoma and quantifying the extent of temporal bone invasion [9].

High definition 4K magnification endoscope and narrow band imaging filter is helpful in visualization of Cholesteatoma. Operative Lighting using Narrow band image (NBI) of wavelength 415 nm and white light image (WLI) of wavelength 540 nm were used for delineating epithelial borders intraoperatively [10].

Discovery of novel immuno-chemical markers of cholesteatoma

Non-Coding RNA (NC RNAs) that form the bulk of cellular RNA (about 98%), specifically an subtype called micro RNAs (miRNAs): MiRNA-27, and let-27, are involved in pathogenesis of Cholesteatoma. This opens targeted pharmacotherapeutic possibilities [11].

Markers Ki-67, cytokeratin 13 (CK13), and cytokeratin 17 (CK17) are immunohistochemical markers found in most Cholesteatoma. Cytokeratin Ki-67 and CK17 are associated with Cholesteatoma and biomarkers of aggressiveness of Cholesteatoma [12]. Other markers of proliferation like Ki-67 (MIB-1), telomerase, transforming growth factor-α, keratinocyte growth factor, and amphiregulin are reported in Cholesteatoma [13]. Markers of inflammation and bone erosion like tumor necrosis factor-α, interleukin-1α, epidermal growth factor, matrix metaloproteinase-9, tenascin, and bone morphogenic proteins have also been reported. Over expression of nuclear factor-κB ligand (RANKL), low expression of osteoprotegerin (OPG) and low RANKL/OPG ratio is related to Middle ear inflammation. KGF and its receptor, MMP-9, KRT-1, KRT-10, and MIF are proposed as biomarkers of recurrence [13].

Imbalance of remodeling markers MMPs MMP-9 and TIMPs TIMP-4 alters transcription of nuclear factor NF-κβ leading to unchecked cellular proliferation. TIMP-4 imbalance is associated with growth of Cholesteatoma. A recent research evaluated the role of a photosensitizer immune conjugate (PIC) specifically cetuximab-benzoporphyrin derivative (Cet-BPD) T-helper cells, and suggested that PICs maybe used for localization of Cholesteatoma intraoperatively [14].

Galectin-7 is DNA genome marker (DNA-aptamer) a molecular imaging, that seems to be helpful in intraoperative visualization of excision margins [15]. d-β-aspartic acid is a detro-beta-isomer of amino acid Aspartic acid found in aging tissue, was found as a sensitive molecular marker for Congenital and Acquired Cholesteatoma but was significantly higher in cystic/sac part of Congenital Cholesteatoma in comparison to surrounding matrix [16].

It is hypothesized that imbalance in T-helper cells 1 versus. T-helper cells 17 ratio causes a self-propagating feedback loop which drives inflammatory diseases like: arthritis, Crohn's disease, or multiple sclerosis. T-helper cells Th1, Th17, M1 cells, and Damage Associated Molecular Patterns (DAMPs), are found in immuno-histological sections of Cholesteatoma, advocating that similar cellular mechanisms seem to be operating in pathogenesis of Cholesteatoma. This has led to hope of molecular targeted therapies (MTT) as a form of Precision medicine for medical therapy of Cholesteatoma [13].

Routes of spread of cholesteatoma

The routes of spread of Cholesteatoma were described by Rosito and Jackler classification are given as follows: 1. Posterior epitympanic, 2. Posterior mesotympanic 3. Anterior epitympanic, 3.Two-route cholesteatoma, and 4.Undetermined cholesteatomas [17].

Developments in Surgical management cholesteatoma

Transcanal endoscopic ear surgery (TEES) is a less invasive surgical option with comparable outcomes in the management of cholesteatoma, congenital cholesteatoma, perforations of the tympanic membrane, and (stapes fixation) otosclerosis and obviates the need for cosmetically inferior postauricular scar [18]. The incidence of residual disease with TEES, appears to be comparable with conventional microscopic technique (6% to 11%). Endoscopic-assisted CWU tympano-mastoidectomy, is a surgical option for recurrent Cholesteatoma [19].

Partial Labyrinthectomy With "Underwater Technique" in which the drilling of Labyrinth is done Submerged under Ringer's solution seems to produce better hearing outcomes due to mitigation of damage to the inner ear environment and neuroepithelium [20].

Recidivism is the tendency for Cholesteatoma to recur despite best surgical effort at ablation. Recidivism is attributed due to Cholesteatoma in the following sites: posterior recesses(Most common), tegmen tympani, Anterior epitympanum, Aditus to antrum and around the Eustachian tube [21].

Conflict of Interest

None.

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