

ORIGINAL ARTICLE

Tympanic Epidermosis: A Noncholesteatomatous Keratinizing Entity of Chronic Otitis Media

Patrice Tran Ba Huy, Romain E Kania, Rania Benhamed, Michel Wassef, Charlotte Hautefort

Department of Otorhinolaryngology-Head and Neck Surgery, Assistance Publique Hôpitaux de Paris, Hôpital Lariboisière, Paris, Université Paris 7 Paris Diderot and LNRS, CNRS 7060 (PTBH, RK, CH)

Department of Pathology, Assistance Publique Hôpitaux de Paris, Hôpital Lariboisière, Paris, Université Paris 7 Paris Diderot (MW)

Department of Otorhinolaryngology-Head and Neck Surgery, Hôpital La Rabta, Tunis (RB)

Objective: Keratin in the middle ear cavity is usually associated with the diagnosis of cholesteatoma currently explained by 3 mechanisms in the literature: retraction, squamous metaplasia and immigration. But different pathogenetic mechanisms cannot result in the same disease. The objective of this study is to show that immigration of the keratinizing epithelium of the tympanic membrane into the middle ear yields a specific entity, tympanic epidermosis.

Materials: Retrospective study of 34 patients referred for "cholesteatoma".

Results: Otoscope findings were mesotympanic perforation lining the malleus handle, keratin surrounding the handle of the malleus and accumulating into the mesotympanum with no limiting matrix, and tympanic remnants opaque and whitish. Histopathology of the tympanic remnants revealed a preserved intermediate fibrous layer lined on both sides by a thin keratinized squamous epithelium. Computed tomography revealed well-ventilated posterior cavities.

Conclusions: Epidemiologic, clinical, pathogenetic, and histopathologic features suggest that immigration of keratinizing epithelium through a mesotympanic perforation results in the clinical condition tympanic epidermosis, which is strikingly different from cholesteatoma and squamous metaplasia. Retraction, metaplasia and immigration processes yield different pathological entities that should be clearly identified, because they do not share the same evolution or require the same therapeutic management.

Submitted : 09 July 2009

Accepted : 20 August 2009

Cholesteatoma developing during the course of a chronic otitis media with perforation is defined by the presence of keratin in the middle ear cavities^[1-7]. Three main mechanisms for such a condition are currently advocated in the literature, namely, squamous metaplasia, retraction and immigration. However, a basic observation is that different pathogenetic mechanisms, hardly any of which are compatible, cannot result in the same disease.

In our series of chronic otitis media referred to our institution with the diagnosis of cholesteatoma, striking epidemiologic, clinical, pathogenetic and histopathological findings were observed in 34

patients leading to the concept of "tympanic epidermosis", an entity that should be clearly distinguished from retraction cholesteatoma and squamous metaplasia.

Patients and Results

The mean age of the 34 patients was 40 years (range 16-76). At presentation, the chief clinical complaints were otorrhea (16 cases), long-lasting and slowly progressive hearing loss (17 cases), otalgia (3 cases), myringoplasty failure (10 cases) and mild vertigo (1 case). All patients had past history of noncholesteatomatous chronic otitis media (COM).

Corresponding address:

Patrice Tran Ba Huy

Department of Otorhinolaryngology-Head and Neck Surgery, Assistance Publique Hôpitaux de Paris Hôpital Lariboisière, 2 rue Ambroise Paré, Paris, France

Phone: 33 1 49 95 66 29; Fax: 33 1 49 95 66 29; Email: romain.kania@lrb.aphp.fr

Copyright 2005 © The Mediterranean Society of Otolaryngology and Audiology

In all instances, otoscopy revealed: i) a partial, subtotal or total perforation of the tympanic membrane lining the handle of the malleus and the umbo; ii) an accumulation of keratin surrounding the handle of the malleus and extending into the mesotympanum; and iii) a thickening and a whitish appearance of the tympanic remnants (Figure 1). Frequently, a mild inflammation of the middle ear epithelium was seen through the perforation.

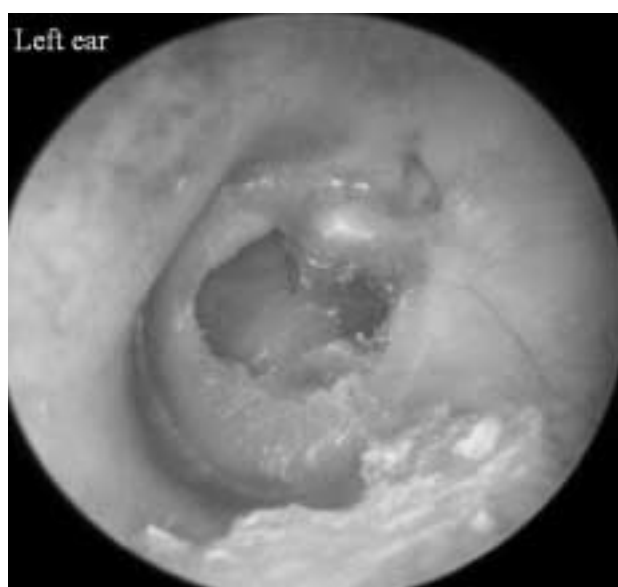


Figure 1. Representative images of tympanic epidermosis. Keratin accumulates in the mesotympanum. Malleus handle is not retracted. The antero-inferior part of the tympanic membrane is opaque.

Tonal audiometry showed a conductive hearing loss, with a mean pure tone average of 40 dB (ranging from 17 to 65 dB) and a mean air-bone gap of 24 dB.

Computed tomography in 14 cases revealed opacity of the mesotympanum, with no evidence of lysis of the bony canal wall. The mastoid was usually well pneumatized and ventilated.

At first, all patients received microaspiration of keratin debris through the perforation and, for those presenting discharge, topical drops or powder for 3 to 4 weeks. This treatment usually yielded a drying of the middle ear cavity and a reduction of the keratosis.

Surgery was performed in 28 of the 34 cases, with the

following observations: i) keratin production originated from the umbo; sometimes an “epidermal crust” attached to the tip of the malleus handle was extracted by aspiration; ii) keratin filled the mesotympanum, extending in some instances in the attic, medially to the malleus head and incus body; iii) a keratinized epithelial layer covered the medial aspect of the tympanic membrane, which had to be sacrificed in most cases; iv) keratin did not adhere to the mucosa and could be easily removed by aspiration; v) no limiting wall could be identified; vi) the middle ear epithelium was frequently moderately inflamed and the ossicular chain appeared normal, except in 3 cases, which showed lysis of the lenticular process of the incus.

After careful removal of all keratin debris, we used a closed technique, with sacrificing the umbo in 9 cases and of the thickened tympanic remnants affected by epidermosis. A temporalis fascia graft was underlaid in 21 cases. A cartilage disk was used in 7 cases when the total surface of the tympanic membrane had to be sacrificed. The ossicular chain was not reconstructed when the incus or malleus handle was missing or removed.

Histological examination of the tympanic remnants removed at surgery showed a preserved intermediate fibrous layer in the tympanic membrane. Both sides of this fibrous layer were lined by a thin keratinized squamous epithelium (Figure 2)

Six patients did not undergo surgery and were followed as out-patients.

The postoperative follow-up ranged from 1 to 8 years. The closure of the eardrum was successful in 26 of 28 cases. In 2 cases, a defect lining the anterior border of the malleus handle was noted at 3 months postoperative. These 2 patients were successfully reoperated. At 1 year postoperative, tonal audiometry showed a mean pure tone average of 28 dB and a mean air-bone gap of 14 dB.

Discussion

Cholesteatoma during COM (thus excluding congenital, traumatic or iatrogenic forms) seems to

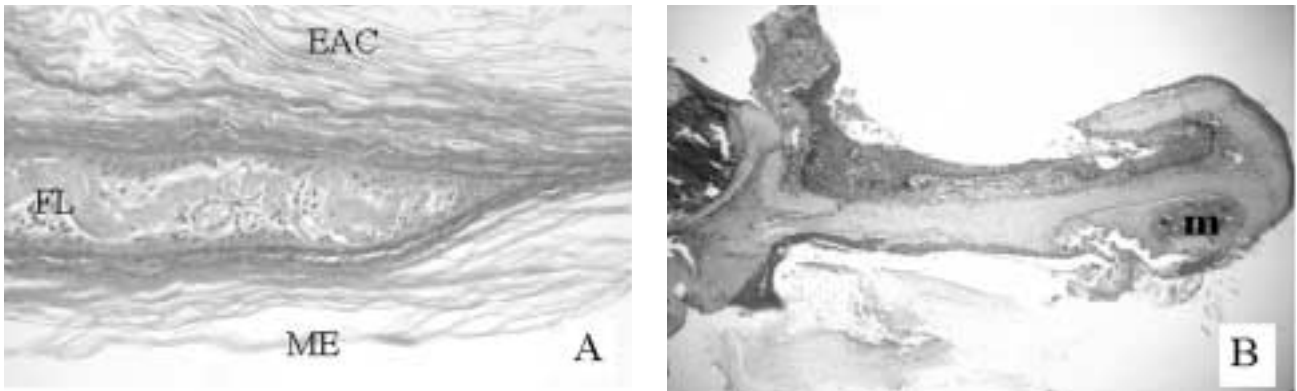


Figure 2. Histopathological appearance of the tympanic remnants. A. Edge of the perforation at a distance from the umbo. The continuity between the squamous epithelium covering both sides of the tympanic membrane is evident (H&E original magnification x 250). B. Section involves the tip of the malleus (m) with the presence of keratinizing squamous epithelium on both sides of the connective fibrous layer.

encompass strikingly different diseases sharing a single feature, the presence of keratin into the middle ear. The 34 cases analysed here were indeed referred with a diagnosis of “cholesteatoma”. Actually, they displayed features specific enough to identify an entity, namely “tympanic epidermosis,” related to a mechanism of immigration and that should be clearly distinguished from retraction cholesteatoma and squamous metaplasia.

Epidemiologic data

Tympanic epidermosis is rare. Among 184 cases with COM referred to our institution during the past 3 years, the condition was identified in 11 cases, for a prevalence of 6%. In the present series, from 1995 to 2004, tympanic epidermosis was observed in 2 main instances. In most of the cases (n=24), the condition developed during long-lasting COM, including mesotympanic perforation, intermittent episodes of purulent otorrhea and mild and ancient conductive hearing loss. In the remaining 10 cases, it was observed after myringoplasty that had been performed for a perforation. These cases were most probably misinterpreted and considered as sequelae. These patients were referred for failure of myringoplasty noted soon after surgery by a dehiscence of the graft near the malleus, through which keratin invaded the mesotympanum. In our series, the mean age of the patients (40 years) was higher than that of patients with cholesteatoma, which, in our last 50 cases of cholesteatoma, then mean age.

Clinical, otoscopic and surgical data

The clinical complaints did not differ from those usually reported by patients (otorrhea or hearing loss) presenting with COM.

From otoscopic and surgical standpoints, consistent findings were a mesotympanic perforation lining the umbo and the malleus handle, and the presence of keratin surrounding the handle of the malleus and accumulating into the mesotympanum. Of relevance is that the tympanic remnants surrounding the perforation were not thin and transparent but, rather, opaque and whitish.

At surgery, keratin debris was found directly on the middle ear mucosa and not surrounded by a cholesteatomatous epithelium, the so-called matrix.

The absence of this limiting epithelium in tympanic epidermosis could account for the remarkable fact that none of the rare but severe complications of cholesteatoma such as facial paralysis or labyrinthitis was observed. Most probably, the lack of this limiting wall prevents an effect of eroding pressure on the surrounding bony structures related to the release of some osteolytic activity^[8-10].

Such findings differ from those encountered with squamous metaplasia and acquired cholesteatoma. Squamous metaplasia presents as whitish spots of keratin, scattered or diffused on the middle-ear mucosa, and no continuity with the tympanic membrane, when remaining. Retraction cholesteatoma

develops specifically in the attic or the postero-superior (much more rarely in the antero-superior) region of the mesotympanum. It usually appears as a whitish or brownish mass corresponding to keratin debris accumulated within a sac. The wall of this sac is continuous with the tympanic membrane. The tympanic membrane is not perforated, unless with repeated infection.

Histopathological data

Examination of the pars tensa sacrificed at surgery shows ^[2] salient features: i) the intermediate fibrous layer is preserved; and ii) squamous epithelium is found on both sides of the tympanic membrane (Figure 3).

Such findings are not observed with squamous metaplasia or retraction cholesteatoma. In squamous metaplasia, the cuboidal pseudo-respiratory epithelium, which lines the middle ear cavity, is focally or extensively replaced by a squamous epithelium having no continuity at all with the perforated tympanic membrane, especially with its squamous epithelial layer. Usually, the metaplastic process forms patchy areas surrounded by nonmetaplastic mucosa with a transitional zone between the two epithelia ^[2,11]. In retraction cholesteatoma, the “matrix” is formed by 2 epithelial layers: a keratinizing squamous epithelium corresponding to the superficial face of the eardrum and a flat cuboidal epithelium similar to that of the medial face of the tympanic membrane. Between them is a very thin, atrophic, poorly organized fibrous layer ^[12], which contrasts with the highly organized fibrous layer found in normal tympanic membrane and tympanic epidermosis. These findings demonstrate that this matrix derives from the exaggeration of a retraction pocket and corresponds to a thinned and distended tympanic membrane deprived of the intermediate collagen layer with accumulating keratin debris.

Pathogenesis of tympanic epidermosis

The accumulation of keratin debris in the middle ear as observed in our series raises the issue of its mechanism.

A congenital origin cannot be put forward since it realizes an epidermal formation occurring behind an intact tympanic membrane and in the absence of a history of otitis media or trauma. Similarly, the theory of papillary ingrowth which holds the fact that local inflammation may induce epidermal basal cells to grow through the lamina propria and to form “cholesteatoma” behind an intact tympanic membrane cannot be retained.

The theory of retraction and of squamous metaplasia ^[13-15] do not fit either with our present observations. The first one suggests that a retraction of a fragile tympanic membrane, either of the pars *tensa* or of the pars *flaccida*, yields the development of a cholesteatoma making it the end result of an atelectatic process. The second one holds the fact that long-standing chronic inflammation of the middle ear mucosa induces histological changes resulting in the replacement of a flat or cubic epithelium with a squamous one ^[2,10]. This squamous metaplasia is, by no means, specific to the middle ear mucosa, because it reflects the ability of different epithelia to alter their differentiation under given conditions ^[16].

A critical appraisal of our cases leads us to consider that none is compatible with the 2 above-mentioned entities: i) perforation of the tympanic membrane precludes any hypopressure and, thus, the development of any atelectatic process; ii) at variance with retraction cholesteatoma, no limiting matrix is found at surgery; iii) the intermediate connective layer of the eardrum is preserved, but its internal face is replaced by a squamous epithelium, never observed in cholesteatoma; iv) middle ear mucosa is inflamed but does not show any whitish spots, which is indicative of a metaplastic process at a distance from the tympanic membrane; v) computed tomography reveals opacity of the mesotympanum corresponding to the keratin debris, but air is found in the mastoid cavity, a feature never found in cholesteatomatous otitis (Figure 3).

Thus, an “immigration” process is the most likely mechanism in our cases. This theory is attributable to Habermann (1888) and Bezold (1890) and holds the fact that stratified squamous epithelium from the

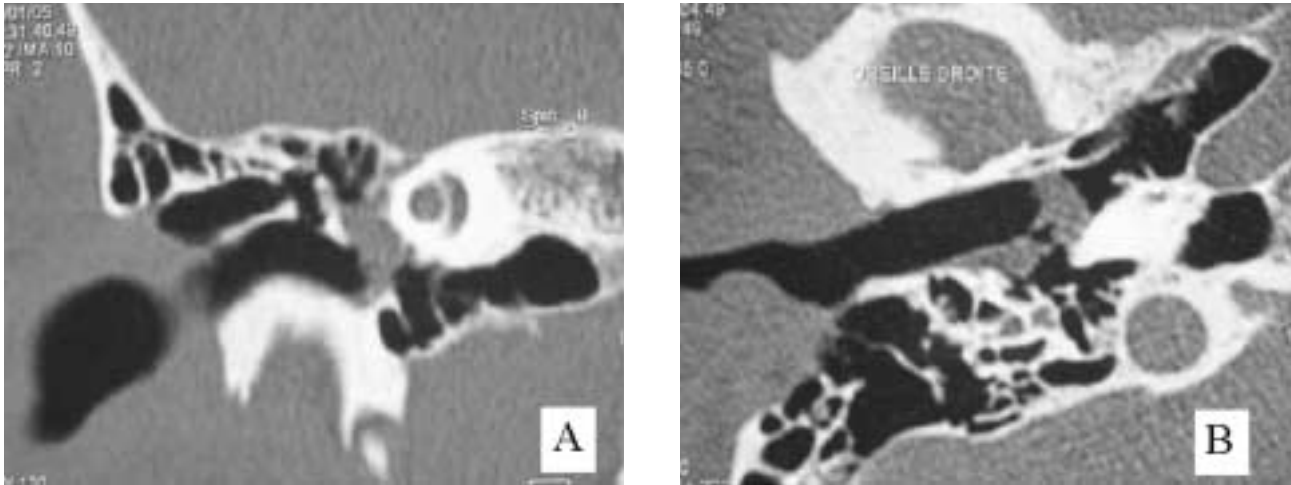


Figure 3. Coronal (A) and axial (B) computed tomography views of the middle ear. The opacity is limited to the mesotympanum. The mastoid and attic are well aerated.

external ear canal may migrate into the middle ear through a marginal perforation of the eardrum^[3]. It implies that the normal direction of canal skin growth, genetically determined to be lateral, is reversed under still unclear pathological conditions^[17], which has never been substantiated by experimental or clinical observations. Most likely, the direction of keratin migration is centrifugal, coming from the umbo and not from the canal skin and progressing through the mesotympanic perforation into the middle ear^[18].

Indeed, immunohistochemical analysis of the keratin types expressed in these lesions could theoretically pinpoint the origin of epidermosis (i.e., external ear squamous epithelium or middle ear mucosa). However, keratin expression is more indicative of the actual differentiation of the epithelium than of its origin^[19].

Therapeutic implications

Medical management includes clearing the debris and powdering the mucosa. Systemic antibiotics are not warranted unless infection with purulent otorrhea is present. Most of the time, local treatment is sufficient to dry up inflammation and decrease keratin production. Such a conservative approach seems justified in older patients because no severe complications are observed in tympanic epidermosis.

Surgery is needed to repair the tympanic membrane or improve hearing loss. Most of the time, surgery

implies sacrificing the rest of the pars tensa and the umbo after disruption of the incudo-stapedial joint to prevent sensorineural impairment. Closure may involve fascia temporalis or cartilage repair.

Clinical significance of keratin into the middle ear

The presence of keratin in the middle ear cavities during COM commonly leads to a diagnosis of cholesteatoma. Actually, when considering the natural history of COM, it may be observed in 3 conditions:

1. An exaggeration of an atelectatic process leading to the localized development of a sac with keratin accumulation and subsequent complications. This type of cholesteatoma is the only condition that should be termed “acquired cholesteatoma.”
2. A long-lasting and severe inflammation of the mucosa lining the middle ear cavities. Here, keratin arises from transformed middle ear epithelium. Actually, this mucosal disease corresponds to squamous metaplasia.
3. An exaggeration of the physiological production of keratinocytes by the umbo by inflammatory stimulation, with secondary invasion of the medial part of the tympanic membrane favored by a mesotympanic perforation lining the malleus handle. This condition corresponds to the immigration theory and leads to accumulation of keratin debris in the middle ear cavity. We termed this entity tympanic epidermosis.

These 3 pathological processes showing different epidemiological, clinical and histopathological characteristics share a unique common feature — the presence of keratin within the middle ear — but rely on different pathogenetic mechanisms. They may be differentiated clinically, and calling all 3 cholesteatoma is misleading^[20]. By analogy, grouping various broncho-pulmonary diseases presenting with expectoration as a common symptom under one denomination is inconceivable.

Conclusion

Tympanic epidermosis represents a variety of COM conditions illustrating the immigration mechanism. It is characterized by a mesotympanic perforation lining the handle of the malleus and the umbo through which keratin diffuses from the umbo into the mesotympanum, with no limiting matrix. Epidemiologic, clinical, physiopathological, and histopathological features distinguish this entity from retraction cholesteatoma and squamous metaplasia. Management is either medical, consisting of local treatment and microaspiration, or surgical, including resection of the umbo, removal of the tympanic membrane and repair by conventional underlay myringoplasty.

Thus, 3 different physiopathological mechanisms, namely immigration, metaplasia and retraction, leading to keratin in the middle ear induce 3 strikingly different disease entities, each characterized by specific features. Clinicians should distinguish among these entities, because they do not share the same evolution nor require the same therapeutic management.

References

1. Sheehy JL. A review of cholesteatoma: 1978-1981. *Am J Otol* 1983; 4:240-250.
2. Sade J, Babiacki A, Pinkus G. The metaplastic and congenital origin of cholesteatoma. *Acta Otolaryngol* 1983; 96:119-129.
3. O'Donoghue GM. The migration theory of cholesteatoma formation. Some experimental observations. *J Laryngol Otol* 1986; 100:395-398.
4. Palva T. The pathogenesis and treatment of cholesteatoma. *Acta Otolaryngol* 1990; 109:323-330.
5. Magnan J, Chays A, Bremond G, et al. [Anatomopathology of cholesteatoma]. *Acta Otorhinolaryngol Belg* 1991; 45:27-34.
6. Sudhoff H, Tos M. Pathogenesis of attic cholesteatoma: clinical and immunohistochemical support for combination of retraction theory and proliferation theory. *Am J Otol* 2000; 21:786-792.
7. Tran Ba Huy P, Aisenberg N. Cholesteatoma and cholesteatomas. Pathophysiological and clinical significance of keratin in the middle ear. In: Ars B, ed. *Pathogenesis of cholesteatoma*. The Hague: Kugler Publications, 1999: 19-35.
8. Sheikholeslam-Zadeh R, Decaestecker C, Delbrouck C, et al. The levels of expression of galectin-3, but not of galectin-1 and galectin-8, correlate with apoptosis in human cholesteatomas. *Laryngoscope* 2001; 111:1042-1047.
9. Sakamoto T, Kondo K, Yamasoba T, et al. Overexpression of ErbB-2 protein in human middle ear cholesteatomas. *Laryngoscope* 2004; 114:1988-1991.
10. Miyao M, Shinoda H, Takahashi S. Caspase-3, caspase-8, and nuclear factor-kappaB expression in human cholesteatoma. *Otol Neurotol* 2006; 27:8-13.
11. Kuijpers W, Vennix PP, Peters TA, et al. Squamous metaplasia of the middle ear epithelium. *Acta Otolaryngol* 1996; 116:293-298.
12. Sade J. Atelectatic tympanic membrane: histologic study. *Ann Otol Rhinol Laryngol* 1993; 102:712-716.
13. Kim HJ, Chole RA. Experimental models of aural cholesteatomas in Mongolian gerbils. *Ann Otol Rhinol Laryngol* 1998; 107:129-134.
14. Meyerhoff WL, Wright CG, Gerken GM. Effects of middle ear ventilation on cholesteatoma development in experimental animals. *Acta Otolaryngol* 1990; 110:279-285.
15. Sade J, Avraham S, Brown M. Atelectasis, retraction pockets and cholesteatoma. *Acta Otolaryngol* 1981; 92:501-512.

16. Sade J. Cellular differentiation of the middle ear lining. *Ann Otol Rhinol Laryngol* 1971; 80:376-383.

17. Makino K, Amatsu M. Epithelial migration on the tympanic membrane and external canal. *Arch Otorhinolaryngol* 1986; 243:39-42.

18. Boedts D, Kuijpers W. Epithelial migration on the tympanic membrane. An experimental study. *Acta Otolaryngol* 1978; 85:248-252.

19. Vennix PP, Kuijpers W, Peters TA, et al. Keratinocyte differentiation in acquired cholesteatoma and perforated tympanic membranes. *Arch Otolaryngol Head Neck Surg* 1996; 122:825-832.

20. Stenfors LE. Does occurrence of keratinizing stratified squamous epithelium in the middle-ear cavity always indicate a cholesteatoma? *J Laryngol Otol* 2004; 118:757-763.

www.balkanorl2010.org

www.balkanorl2010.org



**VII Balkan Congress
of
Otorhinolaryngology
Head and Neck Surgery**

**Serbia, Nis,
10-13 June 2010.**

First Announcement