The associated lesions of cholesteatoma

In this presentation, the authors describe a small group of lesions associated with cholesteatoma, in particular the involvement of its connective component.

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Introduction

In this presentation, the authors describe a small group of lesions associated with cholesteatoma, in particular the involvement of its connective component. Although tympanosclerosis and cholesterol granulomas may be clinically suspect, in general, their microscopic size is dependent on histological identification. All lesions appear inflammatory in nature, be they spontaneous or iatrogenic in case of recurrence. They cannot be isolated from chronic otitis media produced, more or less directly, by the keratinized epithelium. Reversely, they facilitate its progression through mesenchyma-epithelial interactions. Therefore, lesions associated with cholesteatoma are the stimulating and worsening factors of the disease. This implies ample surgical removal, all the more so because some of them are underestimated, as f. i., tympanosclerosis, others are merely ignored, especially owing to their nosologic significance, as keratin or "mixed" granulomas.

Materials and methods

One hundred and four cholesteatomas and 19 retraction pockets were selected from 123 patients, aged 11-76 years, operated on during a period of 18 months.

Specimens were removed during surgery from various middle ear sites, sometimes as a whole (sac and contents), sometimes as punctual biopsies clinically described. These specimens were then fixed with formaldehyde and Bouin's fluid, embedded in cytoparaffin, serially sectioned and stained with routine techniques (hematoxylin eosin, Perls' iron reaction, PAS alcian blue, Masson's trichrome stain) and immunohistochemical stainings to label cytokeratins, vimentin, S 100 protein, T-lymphocyte antigens and leukocyte conunon antigen (LCA) in processed tissues.

Results

It is difficult to histologically differentiate retraction pocket and cholesteatoma. Besides minor grade differences underlined by Zechner', we can mention for the foriner an occasional conservation of elastic fibers and especially the presence of a middle ear cubic or colun-inar epithelium on its reverse.

The sac contents are constituted by flaked anuclear eosinophilic homy material, occasionally by polymorphonuclear leukocytes, macrophages and giant cells surrounding the keratin.

Basically the sac wall ("matrix", Bremond *et al.2)* includes a keratinizing squamous malpighian epithelium ("matrix", Lim and SaunderS3) with four characteristie strata, like epidermis, and a connective tissue stroma ("subepithelial tissue", Kaneko *et al.4;* "perimatrix", Lim and SaunderS3).

As a whole, the epithelium is a rather thin regular lining, devoid of the rete ridges described by various authors, the pegs and papillae being found only near perforations and close to the characteristie spur-shaped advancing edge of the cholesteatoma3,5.

The stroma encloses associated inflammatory lesions giving it a variegated appearance. They

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support and aggravate the advance of the epithelium via a supposed mesenchymal induction. It is noteworthy that just in front of the advancing edge the stroma is generally "bare": an exposed connective area thus separates the original middle ear epithelial liriing from the intrusive epidermis. On the other hand, the latter shows conspicuous localized modifications just above stromal severe inflammatory foci: spongiosis, loss of granular layer, exocytosis, invading Langerhans cells, demonstrated immunohistochemically by LCA and SIOO protein. They lead up to spontaneous epithelial ruptures and confirm the aggressiveness of stromal inflammatory cells towards above-lying epidermiS6. In both situations, granulomatous stroma exposure can facilitate its bulging with an aural polyp appearance.

Associated inflammatory lesions can be classified as follows:

Pseudoglandular hyperplasia (66 cases, 54%)

Pseudoglandular hyperplasia is recognized by gland-like crypts forined by a respiratory type stratified columnar epithelium. These crypts, easily labeled by cytokeratin staining, are more or less deeply located within the stroma. They often undergo cystic degeneration with epithelial fiattening, retention of inspissated mucus, influx of macrophages and sometimes also of polymorphonuclear leukocytes converting them into microabscesses.

Chronie or subacute otitis media (63 cases, 51 %)

Mild or severe lesions are characterized by a non-specific cellular infiltration with polymorphonuclear leukocytes, mastocytes, plasma cells, T lymphocytes and Langerhans histiocytes immunochemically demonstrated and by the development of granulation tissue, moreover associating fibroblasts, newly forined capillaries and focal hemorrhages. This inflammation is localized or diffuse but obviously not confined to the evolutive areas of cholesteatoma6.

Tympanosclerosis (58 cases, 47%, including 50 cholesteatomas and 8 retraction pockets macroscopically noticed in 12 cases)

This lesion can be defined as a partial fibrous change of the stroma, always evoluting to sclerohyalinization with frequent calcifications and possible bone metaplasia or metamorphosis. In our study, we want to stress its rather frequent closeness to macrophagic granulomas.

Macrophagic granulomas (70 cases)

These granulomas are mainly constituted by a congregation of phagocytic histiocytes fusing to form multinucleated giant cells. They proceed from an incitement either by iatrogenous foreign bodies, contamination of the stroma by previous surgery, or by pathologic own middle ear products: cholestatoma keratin and (or) cholesterol.

Giant cells belong to the foreign body type, easily differentiated by staining and nuclei arrangement from tuberculosis Langerhans cells and Wegener's granulomatosis cells.

Cholesterol granuloma (33 cases, 26 %, including 2 retraction pockets)

Recognized macroscopically in 10 cases, it shows each time its well-known histologic components: needle-shaped clefts, moulds of dissolved cholesterol crystals surrounded by slender giant cells and possibly Perls' positive granular brown-yellow hemosiderin deposits (Figs. 2 and 3a).

Keratin granuloma (30 cases, 24 %, including 13 recurrent cholesteatomas and only one retraction pocket)

The homy material is characteristic. Not or weakly birefringent under polarized light, keratin granulomas can be recognized by eosinophilic squames labeled with antikeratin antibodies and by the reaction they activate in the stroma. Sometimes engulfed by macrophages, they are more often located within rounded or irregular slit-like spaces which surround giant cells (Fig. 1). The implantation of keratin flakes can only affect the bare stroma, before advancing, or beneath epithelial gaps (spontaneous or iatrogenic in recurrent cholesteatoma) and is facilitated by pre-existing granulation tissue, edema and vasodilatation as emphasized by Hawke and Jahn7.

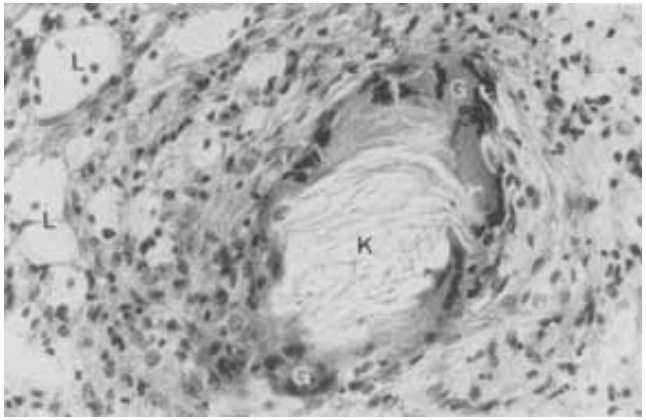

Fig. 1. Small keratin granuloma (woman, *61* years, cholesteatoma). Keratin flakes (K) are surrounded by a rim of multinucleated giant cells (G). L: lipophages. Hematoxylin eosin staining, *400x* (original magnification).
Mixed granulomas (18 cases amongst keratin and cholesterol granulomas)

In this interesting condition, to our knowledge until now not accurately described, cholesterol crystals are closely associated with horny material. Giant cell macrophagic reaction engulfes and surrounds the keratin squames in their irregular spaces, and "geometric" cholesterol clefts (Fig. 2). Moreover, foamy vacuolated lipophages, otherwise found in keratin granuloma (Fig. 1), can complete the granulomatous pattem.

Foreign body granulomas (7 cases, 6%, including 6 cholesteatomas and one retraction pocket) They can be suspected in recurrent cholesteatomas every time the macrophages react against inclusions differing from cholesterol needles and keratin squames. These bodies, hardly noticeable under non-polarized light (Fig. 3a), have a rounded, linear or irregular shape and a glassy or crystalline appearance.

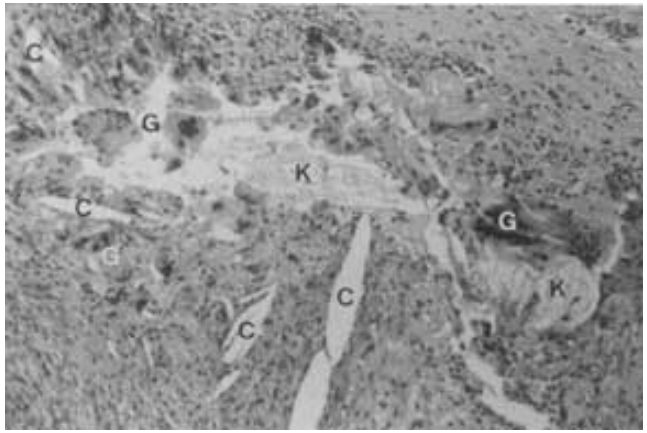

Fig. 2. "Mixed" granuloma (woman, 57 years, cholesteatoma). It shows a conspicuous giant cell macrophagic reaction common to keratin squames (K) and cholesterol crystals (C) (dissolved by histological processing). G: giant cells. Hematoxylin eosin staining, *160x* (original magnification).

Their foreign nature is ascertained thanks to a conspicuous birefringence when examined through crossed polarizing filters (Fig. 3b). They appear to be antibiotic or corticoid deposits, swab threads or prosthetic fragments (one case). On the other hand, the well-known glove starch granuloma was not noticed.

Bone chips (10 cases, 8%)

Irregular necrobiotic bone fragments have been found in the stroma of recurrent cholesteatomas. Clearly distant from its border and unrelated to the small osteitic sequestra of otitis media. They are "chips" removed from temporal bone by previous drilling, and surrounded by fibro-inflammatory reaction with occasional osteoclast-like giant cells.

The squamous epithelium of the cholesteatoma appears as a genuine epidermis by its structure and the presence of skin identifying Langerhans celIS2. It is elosely related to the epithelial lining of the drum outer surface and of the external auditory canal, identically devoid of rete ridges.

Comments

The squamous epithelium of the cholesteatoma appears as a genuine epidermis by its structure and the presence of skin identifying Langerhans celIS2. It is elosely related to the epithelial lining of the drum outer surface and of the external auditory canal, identically devoid of rete ridges.

The stroma is lacking in cutaneous appendages so that the term of skin sometimes given to the cholesteatoma wall is mislabeled and should not be used. Its connective tissue does not derive from the dermis but undoubtedly from the middle ear lamina propria "sensu lato" in eluding the drum fibrous layer. In this way, we can explain the simultaneous presence of both epithelium types, epidennal and tympanic, related to a same connective layer, commonly observed in our slides and also noticed by Lim and SaunderS3, Bremond *et* al.2 and Friedmann8.

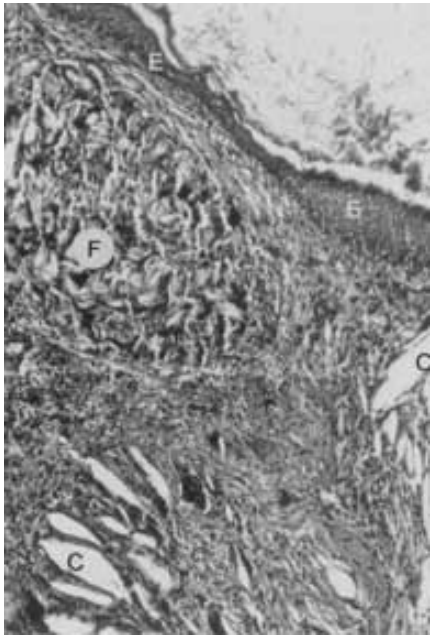

Fig. 3a. Cholesterol granuloma next to a foreign body one (woman, 61 years, cholesteatoma). Polarizing filters uncrossed : foreign particles are not readily visible in their granuloma (F), contrary to cholesterol deposits (C). Hematoxylin eosin staining, 160x (original magnification).

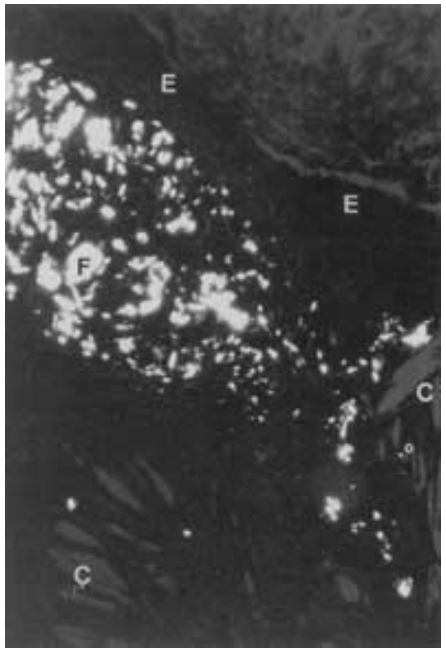

Fig. 3b. Cholesterol granuloma next to a foreign-body one (woman, *61* years, cholesteatoma). Polarizing filters crossed : birefringent foreign

particles (F) are obvious. E : cholesteatoma epidermis. Hematoxylin eosin staining, *160x* (original magnification).

Concerning the pathogenesis of cholesteatoma, our histological observations fundamentally disagree with the metaplasia theory and do not confirm a possible ingrowth of drum epidermis ascertained by R?edi, who supports the direct epidermal immigration theory and, far more accurately, the invagination or retraction pocket theory.

The keratin granuloma is a microscopic entity. It belongs to a variety of ear skin conditions ineluding a common macrophagic reaction to intruded homy material : ventilation tube granuloma7, keratin implantation granuloma9, keratosis obturans, ruptured epidermal and trichilemmomal cysts, inspissated hair, comedo-filled follicle, pilomatricoma. The majority of the authors do not mention or "skim" over this lesion in histological descriptions of cholesteatoma. Hawke and Jahn7 elaborate more on this granuloma considered, however, by them as a trivial foreign body reaction in otitis media.

For their part, Kaneko *et* aL4 and Yuasa *et* al. 10 seem to focus more interest on an osteolytic action of the homy material than on the giant cell granuloma itself, photographed but undescribed as a distinctive lesion in the subepithelial tissue.

In mixed granuloma, the closeness of homy flakes and cholesterol deposits suggests that the **latter** may originate at least partly from lipidic products of keratin breakdown. This hypothesis is reinforced by the frequent presence of "spongy" lipophages in keratin and mixed granulomas and moreover by the observation of cholesterol crystals in ruptured cutaneous epidermal crypts and also in tonsil lymphoepithelial cryptic cysts.

This fact agrees with the tissular cholesterol origin published by Sadé and Teitz" in 1982.

It obviously does not exclude blood cell desintegration as a source of cholesterol, described for a long time8,12 and is in accordance with the frequency of hemorrhages and hemosiderin deposits in pure cholesterol granulomas of our material.

Keratin, cholesterol crystals, accidentally introduced foreign bodies and perhaps also bone chips cannot be removed by efficient phagocytosis. The provoked macrophagic granulomatous reaction becomes persistent, irreversible and perpetuates or increases a neighboring chronic otitis media.

Moreover, tympanosclerosis was found elosely related to giant cell foci in the stroma of several cholesteatomas. Pseudoglandular hyperplasia also enhances otitis media. The crypts are actually pathological structures, themselves a consequence of inflammatory processes13-15.

The middle ear original epithelium may be partly buried within the stroma mainly when an adhesive otitis media is associated.

The cystic degeneration of the pseudoglands may be relevant to an epidermal closure. The cholesteatoma epithelium thus obturates its ostia along the middle ear cavity.

The high rate of tympanosclerosis we noticed is contrary to that of Bremond et aL 16 (7 %) and Plester17 (1%), sometimes asserting that there is a negative association or concurrence between this lesion and cholesteatoma (Gristwood and Venables18).

Our findings assert that histological definition is necessary and that systematic practice of biopsies might be promoted.

Conclusion

The extreme frequency of inflammatory associated lesions of the cholesteatoma stroma, their interlink and the epithelial-subepithelial interactions lead to a large removal of the pathological tissues during chronic otitis surgery.

That means eradication not only of the keratin contents with avoidance of dissemination and obviously of the whole matrix, but also removal of the stroma with its associated lesions as large as possible.

By that way, this work is in accordance with numerous previous publications. Meanwhile our findings especially about the frequency of histological tympanosclerosis and about the existence and the signification of lesions such as keratin granulomas or mixed granulomas need further confirmation and larger series.

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