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Some Remarks on the Histopathology of Otosclerosis

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Abstract

The histopathology of otosclerosis is described in detail in classical textbooks like Schuknecht's *Histopathology of the Ear* or Friedmann and Arnold's *Pathology of the Ear*. In this article, some of the important and new facts will be summarized which might affect the understanding of the pathomechanism of this unique measles-virus-associated inflammatory disease of the temporal bone.

The pathological process of the disease can be summarized as follows: lacunar resorption of the bone by osteoclasts (macrophages), initiated by an unknown pathological, probably viral stimulus affecting the cartilaginous cell nests (globuli interossei) at certain sides of anatomical predilection. The term 'otosclerosis' refers, of course, to the final inactive stage of the process (scar formation), whereas the essential pathological lesion is in fact an inflammatory replacement of the lamellar bone by a bone of greater thickness, cellularity and vascularity. The term 'otospongiosis' refers to the active inflammatory vascular stage of the process. The disease may be present for years without causing deafness. (The histopathology of otosclerosis is described in detail in Schuknecht [1] and Friedmann and Arnold [2].)

The most frequent onset of the progressive hearing impairment has been between the age of 20 and 30; however, today there is a shift to the age of 40 and 50. The histological lesion of the otic capsule begins several years before the onset of stapes ankylosis. The rate of progression depends on the individual, i.e. periods of rapid extension alternating with quiescent phases in some patients, while in others, the lesion steadily progresses. Pregnancy, puberty and the menopause may stimulate the rate of progress probably under the influence of

estrogens [3]. Estrogens are known to activate osteoblasts, so estrogens may have some influence on the otospongiotic lesion changing it into a sclerotic scar. That is why during pregnancy the former otospongiotic lesion near the oval window changes into a sclerotic stage causing conductive hearing loss.

Often a familial disease (30–50%), otosclerosis may be inherited as a mendelian dominant trait and is more common in females: the microscopical incidence of otosclerosis in routine postmortems is about 1 in 8 middle-aged white females, and 1 in 15 adult white males [4]. Histological otosclerosis without symptoms of any kind is about 10 times more common than clinical otosclerosis with stapes fixation producing a conductive hearing loss [5]. In the largest series of temporal bones analyzed to date [4] among 1,161 specimens, 4.39% exhibited otosclerosis. Many of the temporal bones, however, were from black people and it is now well recognized that otosclerosis is rare in the African races. Data collected by Seifer et al. [6] indicated that among 601 temporal bones of white American adults, the histological incidence of otosclerosis was 8.3%. The incidence of stapedial fixation amounted only to 0.99% [7]. Thus, although every 10th adult person has otosclerotic foci within the temporal bone, hearing problems of the conductive type may affect only 1 in every 100 people.

Although any part of the petrous temporal bone may be the side of otosclerosis, the abnormal bone tends to form at particular points, most commonly at the 'otosclerotic angle', which is between the anterior part of the stapedial footplate, the cochleariform process and the bulge of the promontory. By extension posteriorly, this focus infiltrates and fixes the stapes, producing conductive deafness. The entire footplate may be involved, the anterior end only, or both ends, leaving the middle of the footplate intact (fig. 1).

There are certain local anatomical features of the osseous labyrinth, e.g. the fissula ante fenestram and the cartilagenous rests of the enchondral bone of the otic capsule near the oval window, which may offer a locus minoris resistentiae to some inflammatory agents like measles viruses. It should be underlined that more than 90% of all otospongiotic or otosclerotic lesions are in contact with the middle ear mucous membrane as well as with the perilymphatic space (fig. 2a, b).

Otosclerotic foci in other areas of the labyrinthine capsule or in the walls of the internal acoustic meatus can occur simultaneously or in rare cases isolated. In about 70–80% of patients, both temporal bones are affected and the otosclerotic lesions more often than not display a striking similarity in regard to localization, extent and direction of growth. Unilateral histological otosclerosis only occurs in about 20–30%.

The fundamental pathological process of otosclerosis can be summarized as lacunar resorption of the bone by macrophages, initiated by an inflammatory stimulus. Within otospongiotic lesions, a mixed cellular infiltrate can be

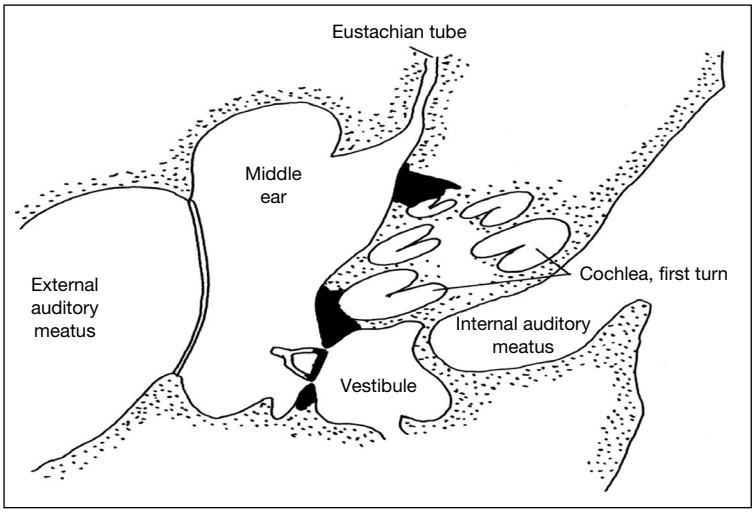
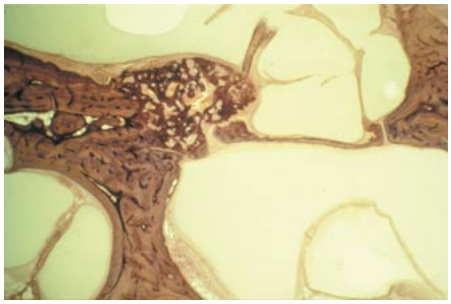
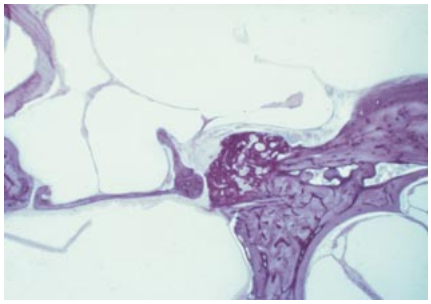


Fig. 1. Sites of predilection of otosclerotic foci (from 2).



a



b

Fig. 2. More than 90% of otosclerotic foci are situated in the oval window area, predominantly in relation to the fissula ante fenestram (asterisk). Also note the relation of the otospongiotic process to the middle ear mucous membrane as well as to the perilymphatic space.

observed, consisting of lymphocytes, macrophages and plasma cells. Macrophages which are capable of presenting antigen in association with major histocompatibility antigens (MHC) class I and class II to CD8+, and CD4+ T-cells, respectively, were found in otospongiotic lesions based on their expression of the MAC387 antigen. Furthermore, HLA-DR-positive cells and complement C3 have been found in resorption lacunae of otosclerotic lesions. Several osteoblasts and chondrocytes in active otosclerotic lesions reveal a strong surface expression of β_2-microglobulin, indicating an increased MHC class I antigen expression in active otosclerotic lesions. In agreement with

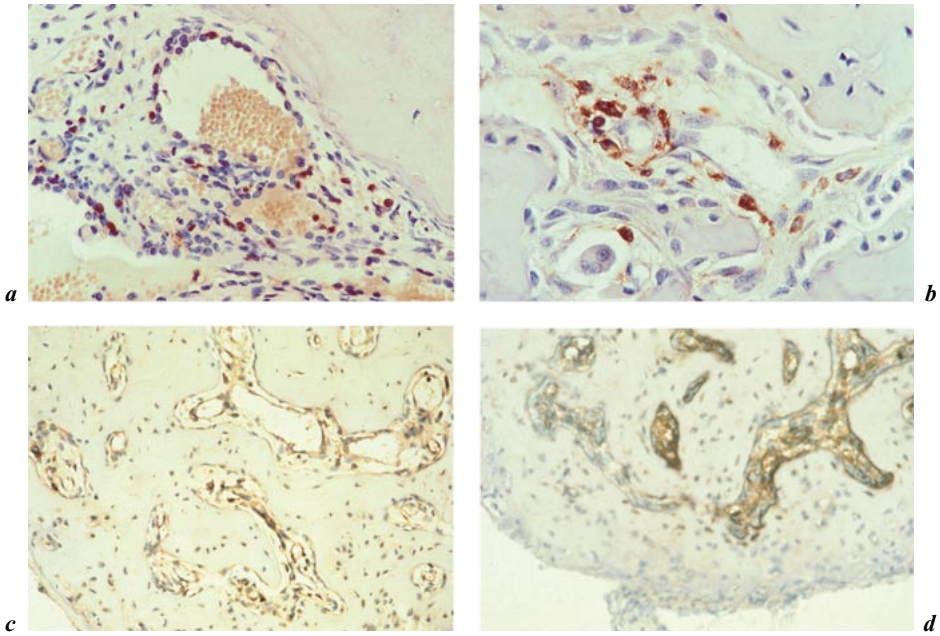


Fig. 3. Infiltration of CD8+ lymphocytes around new vessel formation in a resorption lacuna. Expression of HLA-DR in pervascular macrophages. Expression of β_2-macroglobulin within pericapillary cells. Complement C3 in the perivascular tissue.

recently published data, we found that a large fraction of the lymphoid cells are antigen-primed T-cells expressing an α/β T-cell receptor in association with CD3 molecules on their surfaces. CD4+ lymphocytes which functionally represent lymphokine-secreting cells are activated through the specific recognition of antigen, presented in context with MHC class II molecules such as HLA-DR. Therefore, the presence of MHC-class-II-positive cells is crucial for the initiation of a local immune response. The observation of HLA-DR-positive cells in otospongiotic lesions is of particular interest. Cells expressing the MHC-class-I-associated protein β_2-microglobulin are potential target cells for CD8+ T-lymphocytes which functionally mainly represent cytotoxic T-lymphocytes that are also capable of secreting distinct lymphokines, such as interferon-γ (fig. 3a–d). In this context, the observed strong expression of β_2-microglobulin by osteoblasts and chondrocytes may be of importance for the pathogenesis of otospongiotic lesions. The significance of these findings for an improved understanding of the etiology of otosclerosis remains open, but the findings point at an infectious agent, such as a virus infection, as the primary cause of the inflammatory response of the bone [8–10].

Table 1. Cell type distribution and immunohistochemical reaction of characteristic cell elements within the otospongiotic and otosclerotic focus

	Otospongiosis	Otosclerosis
T-lymphocytes (80%)	+++	–
B-lymphocytes (20%)	++	–
Plasma cells (mainly B-lymphocytes)	++	–
Complement C3 (lytic activity)	+++	–
HLA-DR+ (MHC) (activity of macrophages)	+++	–
β_2-Microglobulin (activation of macrophages)	+++	–
IgG	+++	(+)
IgA	++	–
IgM	–	–
Measles virus antibodies (chondrocytes, osteocytes, perivascular spaces, middle ear mucous membrane)	+++	(−)

What is the factor stimulating the proliferation and aggressive infiltration of the blood vessels (angiogenesis) into the bone of the otic capsule, accompanied by a variety of inflammatory cells including lymphocytes, granulocytes, macrophages and occasional mast cells? The author has examined parts of the footplates from patients at various histological stages of otosclerosis by immunohistochemical methods with particular reference to the distribution of specific antibodies (IgG, IgA, IgM) and the presence and distribution of the viral antigens of measles [9]. Antibodies IgG, IgA and IgM were found to be bound to the vascular connective tissue of the resorption lacunae and IgG also to osteocytes. In specimens showing inactive otosclerosis, no IgG or IgM were present. The active phase of otosclerosis (otospongiosis) appears to be related to IgG fixation (together with C1q and C3 complements), stimulated by a humoral immunological process. The application of antibodies against measles antigens showed the expression of the relevant viral antigens in the large cells of the resorption lacunae, in the vascular connective tissue and in osteocytes, osteoclasts (macrophages) and chondrocytes, present in or around the otospongiotic areas (table 1).

This investigation has provided evidence of the presence of measles virus antigens in all the otospongiotic specimens studied. In contrast, the sclerotic specimens as well as the unaffected parts of the otosclerotic stapes, used as controls, expressed none of the viral antigens. The viral antigens are more strongly expressed by the cells of the perivascular tissue and by various inflammatory cells and macrophages present in the resorption lacunae. This suggests that the

aggressive proliferation of the vascular connective tissue might be initiated in the early stages of otospongiosis and subsequently maintained by the measles viruses. However, otospongiosis today must be respected as an inflammatory, osteolytic bone disease associated with a measles virus infection. There is other unproven but logical support for this pathogenesis as the incidence of otosclerosis has markedly decreased as immunization practices have improved.

This today well-accepted concept of a measles-virus-associated inflammatory disease is supported by recent convincing results from Niedermeyer et al. [11], Lolov et al. [12], Niedermeyer and Arnold [13] and Karosi et al. [14].

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