External ear canal cholesteatoma (EAC) is a rare destructive lesion within temporal bone and may occur in 1:1000 new patients with ear diseases [1, 3]. EAC cholesteatoma was first described by Toynbee in 1850. Since that time, it had confused to keratosis obturans. First description of keratosis obturans was presented by Piepergerdes et al., in 1980 [6]. Keratosis obturans (KO) is a similar to EAC cholesteatoma but separate condition. KO is a plug of cerumen and keratin that occludes the entire ear canal and that cases widening of the bony EAC. In contrast to EAC cholesteatoma, which begins in the inferior part of the bony EAC, keratosis involves the entire circumference of the ear canal and it is frequently bilateral [5]. It occurs in younger patients and so often associated with sinusitis and bronchiectasis. The most common complaints in KO are hearing loss and pain full occlusion [6, 8]. KO is a external ear canal skin disease that may destroy a tympanic membrane, spread into the middle ear cavity and always accompanied by inflammation [8].

Clinically EAC cholesteatoma has the same appearance as middle ear cholesteatoma – a pearlensent ball of skin, more often with surrounding inflammation or granulation tissue. It always involves the inferior part of the ear canal, although it may grow to fill the entire canal [2]. On computed tomographic (CT) imaging, bony erosion of the inferior bony ear canal will usually be seen [3]. In cases with spreading to the mastoid cells, tympanic membrane is often intact and undamaged, a lesion is extending to mastoid due to posterior bony wall of external ear canal destruction and lysis [8].

We used Naim et al. (2005) EAC cholesteatoma classification [4]. This classification is based on histological findings and clinical symptoms. It is known that the cause of congenital EAC cholesteatoma is stenosis of EAC and of spontaneous EAC cholesteatoma is uncertain [12].

The aim of research was to investigate cholesteatoma activity in patients with acquired EAC cholesteatoma based on clinical data, otomicroscopy and high resolution CT scans findings, proteolytic enzymes activity study in middle ear effusion, cholesteatoma matrix and adjacent bone.

**Materials and methods**

11 patients (19-47 years): 9 females and 2 males with acquired EAC cholesteatoma were treated in Ear microsurgery & otoneurosurgery department Otolaryngology State Institution «O. S. Kolomiychenko Institute of Otolaryngology of National Academy of Medical Sciences of Ukraine». Six cases were spontaneous, two cases – postsurgical (after tympanoplasty), two case – post-traumatic, one case – EAC exostosis.

A total of 11 patients who underwent surgery due to EAC cholesteatoma were classified by Naim et al. Stage I – cholesteatoma localized in EAC (n=5), stage II – cholesteatoma localized in EAC and involved ear drum with it’s middle layer preservation (n=4), stage III – cholesteatoma occurs in EAC with adjacent bone destruction and spread to mastoid cells, middle ear cavity is intact (n=2), stage IV – enlarge cholesteatoma with temporal bone involving (n=0).

Otorrhea, hearing impairment and otalgia occurred in all patients before treatment. CT imaging in all 11 cases showed a soft-tissue mass with adjacent bone destruction, in 1 case
with EAC exostosis a soft tissue was shown just behind the exostoses, anteriorly to tympanic membrane. The most common wall invaded by EAC cholesteatoma was inferior wall. The treatment strategy was as follows: stage I – conservative treatment (2 cases), canaloplasty (3 cases); stage II – canaloplasty and tympanoplasty (4 cases); stage III – canaloplasty and mastoidotomy (2 cases).

Tissue homogenates of cholesteatoma matrix and underlying bone of 11 patients with EAC cholesteatoma and 38 patients with middle ear cholesteatoma (20 patients with capsulated for and 18 with diffuse invasive form) were the objects of detailed biochemical investigations. The main proteolytic enzymes (kallikrein, elastase) activity was studied. Elastase and cathepsin B activity was evaluated in ear effusion and middle ear/mastoid mucosa.

About activity of elastase judged for intensities breaking up of chromogenic synthetic peptid of Suc-Ala3-paranitroanilid and expressed in nmol para-nitroanilin, thats labbed from to substrat within 1 hour under the action of 1 mg protein. Activity of kallikrein was determined by the tripeptid of N-Val-Ley-Arg-n-HA and expressed in nmol n-HA/(hour.mg protein).

Results
11 patients were divided due to Naim et al. EAC classification and composed: with stage I – 5 patients, stage II – 4; stage III – 2; no patients with stage IV. Otorrhea, conductive hearing loss, otalgia occurred in all patients. CT imaging in all cases showed a soft-tissue mass with adjacent bone erosion (Fig.). This mass most often arose inferiorly (n=9), inferiorly + posteriorly (n=2). In 6 cases we found a spontaneous EAC cholesteatoma, in 2 cases – post-traumatic, in 2 cases – recurred after previous ear surgery (tympanoplasty), in 1 case – associated with EAC exostosis. In 1 patient in disease history EAC diffuse inflammation was noted. In all cases we found one-side lesion.

Cathepsin B, kallikrein and elastase activity were studied to demonstrate EAC cholesteatoma enzymatic activity and to confirm cholesteatoma matrix proteolytic influence to underlying bone destruction. Biochemical results are demonstrated in Table 1. Enzymatic activity data in cases with EAC cholesteatoma were compared with enzymatic activity in cases with middle ear cholesteatoma.

Table demonstrates a high enzymatic potential in EAC cholesteatoma that may explain a destructive influence to underlying bone. Especially this characteristic well demonstrated on elastase and kallikrein activity – enzymes that lead to main connective tissue protein (collagen) degradation.

Follow-up period in patients with EAC cholesteatoma was composed 28,1months. In 1 case in 14 months after canaloplasty we found residual limited cholesteatoma pearl. This pearl was removed in outpatient department and after that she used polyfunctional proteolytic enzymes inhibitor within 1 months. In 1 patient in 19 months after primary surgery we noted EAC restenosis. This patient was operated on by wide canaloplasty. No extensive residual cholesteatomas in our patients in follow up.

Discussion
EAC cholesteatoma is characterized by aggressive behavior with adjacent external ear canal bone wall destruction [1-6, 9, 12, 13]. Such aggressive behavior may explain by high proteolytic enzymes activity in cholesteatoma matrix. The main principle of treatment for EAC cholesteatoma is surgical removal of cholesteatoma, necrotic bone tissue to prevent dis-
ease spreading and bone destruction with preservation of the normal external auditory canal skin. Exact borders for affected EAC bone removing are distinguished by the high resolution CT scans imaging with determination of bone necrosis and bone erosion zones. Thus, in stage I conservative local treatment is proposed as a method of choice and composed of cholesteatoma debris removal with aspirator with aftercare by using local ear drops [13], application of Burow’s liquid [10] or surgical treatment – canaloplasty with maximal normal skin preservation [12, 13]. Canaloplasty with tympanoplasty are considered in cases with tympanic membrane damage and more suitable for stage II. When the lesion invades the mastoid air cells as defined by stage III, the patient can be operated on by canaloplasty, mastoidotom and optional tympanotomy. In the stage III cases, reconstruction of the EAC wall can be performed with bone dust (“bone pate”). In stage IV with EAC cholesteatoma spreading beyond the temporal bone, the cholesteatoma should be removed via various suitable approaches [7]. Naim et al. EAC cholesteatoma classification could be applied only to preoperative evaluation and seen unsuitable for postsurgical period to evaluate residual disease [4].

### Proteinazes activity in ear effusion, bone, cholesteatoma matrix and middle ear mucosa in patients with EAC cholesteatoma and middle ear cholesteatoma

<table>
<thead>
<tr>
<th>Object</th>
<th>Proteazes</th>
<th>Lesions</th>
<th>EAC cholesteatoma (n=11)</th>
<th>Incapsulated cholesteatoma (n=20)</th>
<th>Diffuse cholesteatoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear effusion</td>
<td>Cathepsin B</td>
<td>64,8 ± 4,1</td>
<td>22,5 ± 4,3</td>
<td>83,0 ± 10,0 p&lt;0,01</td>
<td>56,0 ± 5,7</td>
</tr>
<tr>
<td></td>
<td>Elastase</td>
<td>129,2 ± 21,4</td>
<td>48,0 ± 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>Elastase</td>
<td>71,4 ± 7,1</td>
<td>28,0 ± 2,4</td>
<td>52,0 ± 6,1</td>
<td></td>
</tr>
<tr>
<td>Adjacent bone</td>
<td>Kallikrein</td>
<td>389,0 ± 82</td>
<td>119,0 ± 21,0</td>
<td>444,0±100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elastase</td>
<td>78,5 ± 6,8</td>
<td>20,0 ± 3,5</td>
<td>31,0±9,3</td>
<td></td>
</tr>
<tr>
<td>Cholesteatoma matrix</td>
<td>Kallikrein</td>
<td>211,0±38</td>
<td>150,0 ± 24,0</td>
<td>238,0±71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elastase</td>
<td>21,0 ± 2,1</td>
<td>12,0 ± 4,0</td>
<td>22,0±4,9</td>
<td></td>
</tr>
</tbody>
</table>

*p* – statistically differencies in biochemical data in patients with EAC cholesteatoma, incapsulated and diffuse cholesteatoma

Preoperative high resolution CT scan is essential in defining the extent of lesion. High resolution temporal bone CT scans shows EAC cholesteatoma as a soft-tissue mass within the EAC with adjacent bone erosion. The most common destructive lesions are noted in the inferior EAC wall. High enzymatic proteolytic potential in common objects (cholesteatoma matrix, underlying bone, middle ear effusion) in patients with EAC cholesteatoma was statistically higher than in patients with incapsulated (less aggressive) middle ear cholesteatoma and was statistically similar to diffuse aggressive middle ear cholesteatoma. Conservative treatment seen to be possible only on limited small EAC cholesteatomas without imaging signs of adjacent bone destruction. In cases with destructive bone lesions – surgical treatment is a method of choice. Canaloplasty with maximal normal undamaged external ear canal skin preservation should be performed in all cases with bone erosion. In cases with total skin damage canaloplasty with free skin flap reconstruction should be performed. Such clinical approach should minimize a risk of residual cholesteatoma formation. Due to our data cathepsin B evaluation in ear effusion should be consider as a marker of cholesteatoma aggressivity. That test could be used as in preoperative diagnostic and in follow-up as well. Polyfunctional proteolytic enzymes inhibitor in the treatment of limited EAC cholesteatoma – perspective issue due to prevention of destructive influence cholesteatoma matrix enzymes to adjacent external ear canal bone walls that should be exclude a necessity of
surgical procedures. In follow up and long term follow up high resolution CT scan should be used in combination with diffusion-weighted magnetic resonance imaging (DWIMRI) to recognize residual or recurrent disease.


ТАКТИКА ЛІКУВАННЯ ПРИ ХОЛЕСТЕАТОМІ ЗОВНІШНЬОГО СЛУХОВОГО ПРОХОДУ

Співавтор І.А. (Київ)

Р е з ю м е

Характерною особливістю холестеатоми вважається скупчення кератинизованого сквамозного епітелію в нетиповому для нього місці, котре в межах скроневої кістки може виявлятися в середньому вусі, піраміді скроневої кістки та зовнішньому слуховому проході. При холестеатомі зовнішнього слухового проходу (ХЗСП) визначено високий ензиматичний потенціал, чим може пояснюватися її деструктивний вплив на підлеглу кісткову тканину. Особливо це стосується активності ферментів, які призводять до деградації основного білку сполучної тканини.

Ключові слова: холестеатома зовнішнього слухового проходу, ферментативна активність, протеолітичні ферменти, калікреїн, еластаза, катепсин В.
MANAGEMENT OF EXTERNAL AUDITORY CANAL CHOLESTEATOMA

Srebniak I. (Kiev)

Resume

Stratified keratinized squamous epithelium accumulation in atypical for that place within temporal bone may occur in the middle ear, petrous apex and the external ear canal. That may interpreted as a “wrong skin in the wrong place” and is a common feature of cholesteatoma. The main pathogenetic substrate of cholesteatoma is an adjacent bone destruction. The most common site for cholesteatoma localization is a middle ear cavity and by some authors is represented as a complicated form of chronic otitis media. External auditory canal (EAC) is a rare place of cholesteatoma formation. The lesion typically presents otorrhea, otalgia (chronic dull pain), local invasion into the bony EAC. Etiology and pathogenesis have not yet been established. The cause of destructive damaging of adjacent external canal bone in cases of cholesteatoma also unknown. We evaluated clinical features of EAC cholesteatoma, it’s enzymatic activity in matrix and adjacent bone in 11 patients in comparison with 20 patients with encapsulated middle ear cholesteatoma and 18 patients with diffuse aggressive middle ear cholesteatoma. Aggressive behavior of EAC cholesteatoma was established in the main group of patients based on its high enzymatic activity that was characterized by significant destructive influence on adjacent bone walls. High proteolytic enzymes (kallikrein, elastase, cathepsin B) activity levels were determined as in cholesteatoma matrix, as in adjacent bone wall – significantly similar with enzymatic activity in patients with diffuse aggressive middle ear cholesteatoma. Cathepsin B could be used as a marker of cholesteatoma aggressiveness in patients with EAC cholesteatoma and might be a prognostic factor in cholesteatoma behavior.

Keywords: external ear canal cholesteatoma, enzymatic activity, proteolytic enzymes, kallikrein, elastase, cathepsin B.