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Case study

Mixed epithelial and stromal tumor of the middle ear. The first case report☆,☆☆

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Summary We report a tumor arising in the middle ear of a 65-year-old female patient that was composed of an ovarian-type stroma (OS) and an epithelial component. The tumor consisted of irregular, polypoid masses containing multiple variably sized cystic spaces, which were invariably surrounded by the OS. The cystic spaces were lined by flat, cuboidal, or columnar epithelial cells, in most parts showing mucinous differentiation. The epithelial lining of the cysts strongly expressed cytokeratins AE1-3, CK7, CK8, CK18, CK19, EMA, and S100 protein. The stroma expressed CD34 and smooth muscle actin. No cytological atypia or mitoses were present, and the proliferative activity was less than 1% in both components. The clonality analysis proved the clonal nature of the neoplasm. We believe that this tumor is a new member in the family of neoplasms containing the OS, and therefore we propose the term *mixed epithelial and stromal tumor of the middle ear*.

1. Introduction

It is well known that ovarian-type stroma (OS) (along with an epithelial component) may occur in a variety of tumors outside the ovary. The best known examples are mucinous cystic neoplasms of the pancreas, liver, and biliary system [1-4]. Rarely, similar tumors can also develop in the retroperitoneum [5,6], spleen, mesentery [7], or vicinity of the testis [8,9]. Another example include the mixed epithelial and stromal tumor (MEST) of the kidney, originally described by one of the authors (Michal M.) [10,11]. The tumors containing OS show a striking female predilection.

Herein we present a unique case of a tumor arising in the middle ear of an adult woman that featured both OS and an epithelial component. By analogy to its renal counterpart, we designated the neoplasm benign *mixed epithelial and stromal tumor of the middle ear* (MESTME). We are unaware of any published reports of a similar neoplasm in this location.

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2. Case report

2.1. Clinical findings

A 65-year-old woman suffering from chronic inflammation of the middle ear and a long-standing partial hearing loss complained of further rapid decline in the quality of perception in her right ear and occasional vertigo. The phoniatric and vestibular testing proved that her right ear is completely nonfunctioning in both auditory and vestibular components. On otoscopy, the upper part of her right tympanic membrane showed a prominent bulging. Middle ear polyp was suspected, and the patient was scheduled for an explorative tympanotomy. During the operation, a rounded polypoid tissue that occupied the entire middle ear cavity and separated the auditory bones was resected. The histological diagnosis of chronic hyperplastic medial otitis with prominent metaplastic changes was rendered.

In the following 3½ years, the patients' clinical course was unremarkable. Eventually, at a regular ear-nose-throat examination, the right tympanic membrane otoscopically showed similar recurring exophytic bulgings, which were excised. The subsequent histological diagnosis was identical to the original one.

Three years after the second operation, the patient remains without any signs of recurrence.

2.2. Radiologic findings

The preoperative computed tomographic (CT) scan from 2009 showed in bone window complete obliteration of right mastoid air cells and cavum tympani with a dense content. There was no destruction or reactive sclerosis of the surrounding bone. The septa between the air cells were slightly thickened (Fig. 1A). The preoperative CT scan from 2013 showed a mild thickening of the residual septa in the right mastoid after a middle ear surgery and mastoidectomy. Again, the presence of a dense content in residual mastoid air cells and cavum tympani can be seen. However, it could not be reliably distinguished whether it was a tumorous or a mucous mass. There was no destruction of the surrounding bone, and the very subtle sclerosis was most likely postoperative (Fig. 1B).

2.3. Pathological findings

Macroscopically, the first specimen consisted of 3 irregular, partially fragmented samples of tissue, each of them no larger than 1 cm in the largest dimension. The second specimen obtained 3½ years later was grossly composed entirely of fragmented tissue, together measuring 2 cm in the largest dimension. Histologically, both tumors were identical (Figs. 2 and 3). They consisted of irregular, polypoid masses containing multiple variably sized cystic spaces lined by flat, cuboidal, or columnar epithelial cells, in most parts showing mucinous differentiation with occasional goblet cells. The lumina of many cysts were filled with an eosinophilic secretion. The cysts were invariably surrounded by the OS, focally with variably pronounced hyalinization. In several parts of the stroma, areas strongly resembling corpora albicantia were encountered (Fig. 3C). Clusters of variably sized mucinous or seromucinous glands were scattered throughout the OS. In some parts, the tumor featured a squamous epithelium. As a rule, no cytological atypia or mitoses were present.

Immunohistochemical features are summarized in the Table. The epithelial lining of the cysts strongly expressed cytokeratins AE1-3, CK7, CK8, CK18, and CK19 and epithelial membrane antigen (EMA). Epithelial cells in a small proportion of the cysts expressed S100 protein. The stromal cells were reactive with CD34 protein and in some parts expressed smooth muscle actin. Scattered, weak expression of progesterone receptors (PRs) was noted focally (Fig. 3D). Estrogen receptors (ERs), calponin, inhibin, desmin, CD56, HMB45, TLE-1, CK20, CD-X2, MUC 2, MUC 5AC, MUC 6, antimucin monoclonal antibody, and PAX-8 were completely negative. MIB1 antibody was positive only in exceptional cells (less than 1% in both components).

2.4. Molecular genetic findings

2.4.1. *SYT* gene break

Molecular studies were performed to exclude biphasic synovial sarcoma using a previously described method [12], and the neoplastic sample was negative for an *SYT* gene break.

2.4.2. Clonality analysis using X-chromosomal inactivation pattern and human androgen receptor locus

The clonality analysis was performed according to a previously described method [13]. Analysis of tumor tissue revealed clonality ratio of 0.15 indicating its monoclonal pattern.

2.4.3. Detection of the NAB2-STAT6 fusion transcript by reverse-transcription polymerase chain reaction

RNA was extracted using the RecoverAll Total Nucleic Acid Isolation Kit (Ambion, Austin, TX). cDNA was synthesized using the Transcriptor First Strand cDNA Synthesis Kit (RNA input 500 ng) (Roche Diagnostics, Mannheim, Germany). All procedures were performed according to the manufacturer's protocols. Amplification of a 105– and 133–base pair product of the *B2M* gene and 247–base pair product of the *PGK* gene was used to test the quality of the extracted RNA as previously described [14,15]. For the detection of the *NAB2-STAT6* fusion transcript using reverse-transcription polymerase chain reaction (PCR), the same combination of the primers in *NAB2* and *STAT6* genes as described previously was applied [16].

For PCR, 2 mL of cDNA was added to reaction consisting of 12.5 mL of HotStar Taq PCR Master Mix (Qiagen, Hilden, Germany), 10 pmol of each primer, and distilled water up to 25 mL. The amplification program comprised denaturation at 95°C for 14 minutes and then 45 cycles of denaturation at 95°C for 1 minute, annealing at 60°C for 1 minute, and extension at 72°C for 1 minute. The program was finished