Carcinoid Tumor of the Middle Ear in a 28-Year-Old Patient

Hendrik BLÄKER,1 Gerhard DYCKHOFF,2 Hagen WEIDAUER,2 Herwart F OTTO1

1Department of Pathology, 2Department of Otorhinolaryngology, University of Heidelberg, Heidelberg, Germany

Carcinoid tumor of the middle ear is an extremely rare condition. The origin of the tumor cells is still speculative and the closeness of relationship to adenomas of the middle ear has been a matter of discussion since the first description of this tumor entity in 1980. In this study we report a case of a 28-year-old male patient with a carcinoid tumor of the middle ear. We present the results of histomorphological, immunohistochemical and electron microscopic examinations and compare our findings to those of previously published cases. (Pathology Oncology Research Vol 4, No 1, 40–43, 1998)

Key words: carcinoid, tumor, pathology, diagnosis, middle-ear

Introduction

Carcinoid tumors of the middle ear are rare. To the best of the authors’ knowledge less than 40 cases were published since Murphy et al16 described the first tumor of this entity. Clinical features often present as local symptoms caused by the tumor growth like hearing loss, tinnitus or fullness of the ear whereas typical carcinoid symptoms are rarely described.16,17

The origin of the tumor cells is still speculative. Although the tympanic cavity derives from the embryonic foregut which is supplied with abundant neuroendocrine cells, these cells have not been found in the regular tympanic cavity10 and could only be demonstrated in hypertrophic epithelium in close vicinity of a middle ear carcinoid.3

In this report we describe a case of a 28-year-old male patient with a carcinoid tumor of the middle ear, present the findings revealed by light microscopy, immunohistochemistry and electron microscopy and compare our results to the data collected from previously published cases.

Clinical history

A 28-year-old male patient complained of tinnitus and progresdant slight hearing loss of the left ear. His previous history mentioned a left-sided tympanic effusion which had been treated by myringotomy and drainage of the tympanic cavity a year earlier. On admission, otoscopy revealed a retracted left tympanic membrane and audiometry showed a conductive hearing loss of 10 dB. Binocular microscopic evaluation of the eardrum revealed a smoothly-surfacesed tumorous mass in the left tympanic cavity. Magnetic resonance scanning of the middle ear demonstrated an expansive growth of the tumor into the Eustachian tube (Figure 1). A tympanotomy was performed and the tumor was removed completely.

Pathology

Histologically the tumor revealed a mixed pattern with solid structures and cell nests on the one hand and an adenomatous aspect with tubular glandular formations on the other hand (Figure 2). Occasionally rosette-like patterns of differentiation were seen. „Zellballen" were not observed. The tumor cells were generally isomorphic and polygonal with a broad and eosinophilic cytoplasm. The basophilic nuclei were round and sometimes oval in shape. Mitotic figures could not be detected. PAS staining was positive in the glandular spaces formed by the tubular structures of the tumor indicating the presence of mucus in...
most of the tumor cells were intensely positive for cytokeratin (K11, A1 and 3, Figure 3B), vimentin, chromogranin A and neuron-specific enolase. Protein S-100 staining was seen predominantly in sections with a more solid character whereas serotonin and pancreatic polypeptide were mainly detected in the cells of the tubular formations (Figure 3A,C). Cells with anti-PP staining were fewer in number and showed a finer granular staining than those with anti-serotonin staining. Both cell types exhibited a very strong resemblance as far as distribution and morphology were concerned. Coexpression of both hormones could not be investigated for the immunohistochemical reactions were performed on different sections. No significant reaction was obtained for neurofilaments and the other neuroendocrine hormones tested (glucagon, insulin, somatostatin and VIP). Electron microscopy revealed abundant secretory granules of an average diameter of 250 nm. They were similar in shape but showed a heterogeneous degree of density (Figure 4A). Additionally, intermediate filaments arranged in a bundle-like manner were found in the intergranular spaces (Figure 4B).

**Discussion**

The light microscopic distinction between carcinoids and other tumors of the middle ear, especially adenomas, can be very difficult. In our case the light microscopic aspect of the tumor mainly helped to rule out a parangangioma which can occur at this location but is characterized by „Zellballen” and a typical vascular component.

For differential diagnostic purposes of tumors of the middle ear Krouse et al. have published a valuable list of findings to be expected in primary carcinoids. These find-
ings include a positive Grimelius stain, detection of neurosecretory granules by electron microscopy, and positive immunohistochemistry for serotonin, neuron-specific enolase and cytokeratins AE-1 and AE-3. Except for the Grimelius stain which was not applied in our case the tumor of our patient fulfilled all of the proposed criteria. Additionally we obtained a positive immunohistochemical result for vimentin as it is described in all previous cases in which the suitable investigation was undertaken.\textsuperscript{3,4} We also detected chromogranin A and protein S-100. These findings are reported in previous studies\textsuperscript{3,5,6,11,12,14,15,19} and may contribute to diagnosis because chromogranin A is regularly seen in carcinoids independent of their location\textsuperscript{11,22} and anti S-100 staining was reported for carcinoid tumors in general by Nakajima et al.\textsuperscript{17}

In our tumor sample the cells which stained with the antibody against pancreatic polypeptide were fewer in number than those with anti-serotonin staining indicating the predominance of the latter type of endocrine activity. Nevertheless, the existence of pancreatic polypeptide in middle ear carcinoid tumor cells is described in all cases in which the specific antibody was applied.\textsuperscript{1,2,3,7,14,18,21} Therefore immunoreactivity to pancreatic polypeptide seems to be more specific to the middle ear carcinoid than immunoreactivity to serotonin which was reported to be negative in a few investigated cases.\textsuperscript{3,12,15,21} Beside the detection of serotonin and pancreatic polypeptide Azzoni et al\textsuperscript{1} found immunoreactivity for glucagon and alpha HCG in a few cells of two investigated middle ear carcinoids. A review of literature reveals other cases in which additional peptide hormones were detected.\textsuperscript{2,19,20} Our results based on an immunohistochemical study which did not include all possibly detectable hormones (Table 1) and did not indicate the production of further peptides by the tumor cells.

The existence of both neuroendocrine and epithelial exocrine cells in the same tumor sample indicates a biphasic differential capability. Faverly et al\textsuperscript{4} and Manni et al\textsuperscript{13} reported four cases of middle ear carcinoids and distinguished between neuroendocrine B-cells and exocrine A-cells. The latter cell type had the appearance of endothelial cells and showed a very intense staining with cytokeratin. In their tumor samples they found a third amphicrine cell-type characterized by the coexistence of neuroendocrine

\textbf{Figure 3.} Immunohistochemistry in a section with predominant tubular formations, for (A) pancreatic polypeptide with a fine granular staining, (B) Cytokeratin KLT, and (C) Serotonin – (A) \textit{x630}, (B) \textit{x200}, (C) \textit{x320}

\textbf{Figure 4.} Ultrastructure of the tumor cells. Detection of (A) abundant neuroendocrine granules with different degrees of density, and (B) intermediate filaments arranged in bundles – (A) \textit{x12000}, (B) \textit{x13000}
granules and exocrine lumina in its cytoplasm. This cell
type was considered to be a link between A and B cells.
In our case we did see a predominant neuroendocrine
differentiation (B-cells). Although exocrine cells resembling
the description of A-cells could not be found, exocrine activity
was indicated by PAS-positive material in the lumina of the
tubular glandular formations. Additionally the evaluation
of the semi-thin sections showing cells with either
neurosecretory granules or intracellular lumina indicates
the existence of an amphiicrine cell type.

In conclusion, the results we present herein are in line
with the findings of Faverly et al and support the idea that
carcinoid tumors of the middle ear derive from a pluripotent
uncommitted stem cell with biphasic differentiable capability.

Literature

endocrine tumours of the middle ear and of the sinuses have
immunocytochemical and ultrastructural features in common.
2. Davies JE, Seneraro D, Knight LC, et al: Middle ear neo-
plasms showing adenomatous and neuroendocrine components.
middle ear and endolymphatic sac. Pathol Annual 29 (Part
amphiicrine tumors of the middle ear: a new entity? Path Res
5. Hale RJ, McMahon RFT, Whittaker JS: Middle ear adenoma:
Tumour of mixed mucinous and neuroendocrine differentiation.
middle ear containing serotonin and multiple peptide hormones.
8. Krouse JH, Nadol JB, Goodman ML: Carcinoid tumors of the
9. Latif MA, Madders DJ, Barton RPE, et al: Carcinoid of the
middle ear associated with systemic symptoms. J Laryng Otol
10. Lim DJ, Birck H: Ultrastructural pathology of the middle ear
mucosa in serous otitis media. Ann Otol Rhinol Laryngol
localization of epinephrine, norepinephrine, catecholamine-
synthesizing enzymes, and Chromogranin A in neuroendocrine
tumor of the jugulotympanic area. J Nucl Med 37:270-272,
1996.
13. Manni JJ, Faverly DRGS, van Haelst UJGM: Primary carcinoid
tumors of the middle ear. Arch Otolaryngol Head Neck Surg
Mittelohres: Seltener Tumor mit biphasischer Differenzierung.
An ultrastructural and immunocytochemical study. Am J Clin
16. Murphy GF, Pilch BZ, Dickersin GR, et al: Carcinoid tumour of
study of S-100 protein distribution in normal and neoplastic tis-
18. Ruck P, Pfister EM, Kaiserling E: Carcinoid tumour of the
middle ear: A morphological and immunohistochemical study
with comments on histogenesis and differential diagnosis. Path
middle ear: an immunohistochemical and electronmicroscopic
gastroenteropancreatic neuroendocrine cells in normal and neop-
lastic human tissue with antibodies against synaptophysin,
chromogranin A, secretogranin I (chromogranin B), and secre-