CASE REPORT

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

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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 al[16] 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 symtpoms are rarely described.[1,9,16]

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 cavity[10] 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.

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Clinical history

A 28-year-old male patient complained of tinnitus and progredient 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-surfaced 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

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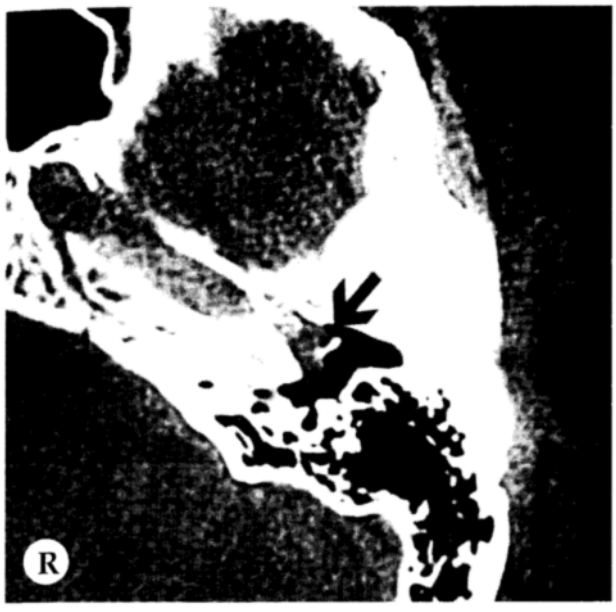

Figure 1. Magnetic resonance scanning of the left middle ear. The tumorous mass in the tympanic cavity is indicated by an arrow. The pneumatization of the tympanic cavity and the neighbouring mastoid cells is still regular.

this areas. Intracellular staining with PAS was not observed. A semi-thin section showed a tubular formation in the center of a solid tumor area *(Figure 2B)*. At the basal pole of the cells forming the tubulus abundant secretory granules were seen. Some of these cells also contained additional intracellular lumina predominantly located at the apical pole and the tubular lumen was filled with an amorphic, secretory material. Immunohistochemically most of the tumor cells were intensely positive for cytokeratin (Kl1, 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 heterogenous 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 paraganglioma 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[8] have published a valuable list of findings to be expected in primary carcinoids. These find-

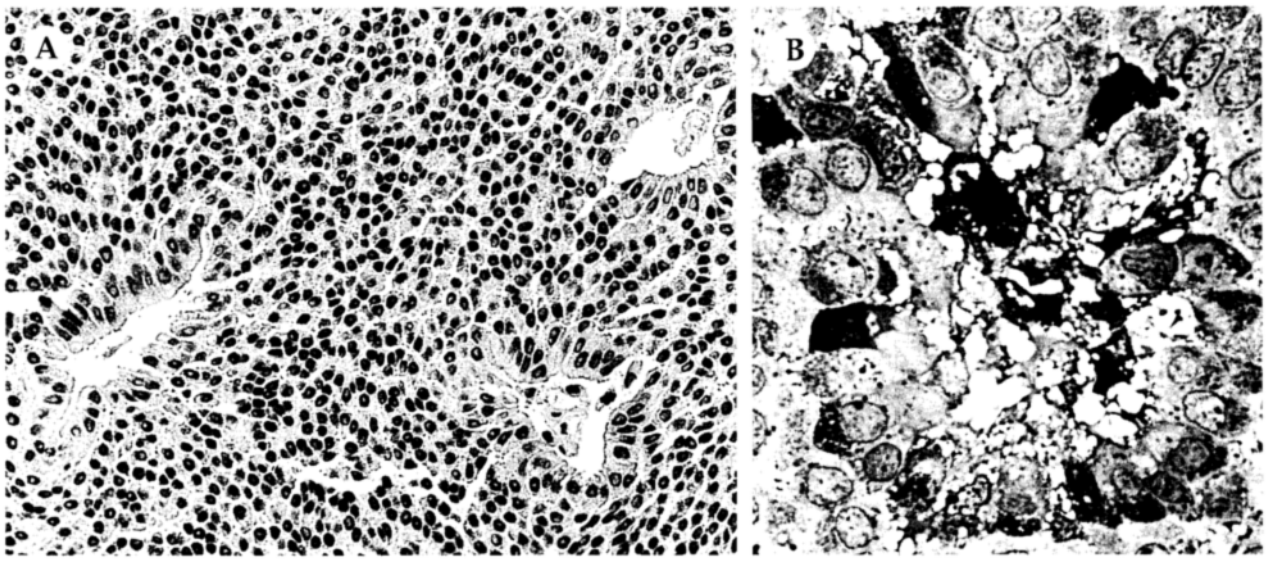

Figure 2. Histological structure of the tumor showing (A) the mixed solid and tubular-glandular pattern, H&E, x300 and (B) cells of a tubular formation with either lumina and/or neurosecretory granules, semi thin section, methylene blue and eosin, x1800.

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.[3,14] We also detected chromogranin A and protein S-100. These findings are reported in previous studies[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[11,22] and anti S-100 staining was reported for carcinoid tumors in general by Nakajima et al.[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.[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.[3,12,15,21] Beside the detection of serotonin and pancreatic polypeptide Azzoni et al[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.[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.

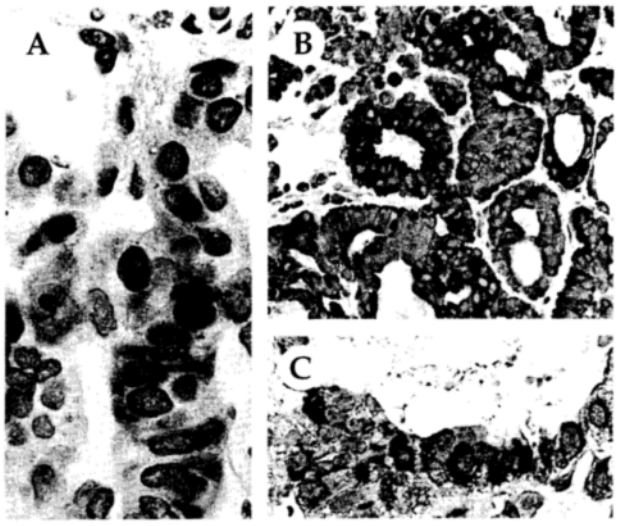

Figure 3. *Immunohistochemistry in a section with predominant tubular formations, for (A) pancreatic polypeptide with a fine granular staining, (B) Cytokeratin KL1, and (C) Serotonin – (A) x630, (B) x200, (C) x320*

The existence of both neuroendocrine and epithelial exocrine cells in the same tumor sample indicates a biphasic differential capability. Faverly et al[4] and Manni et al[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

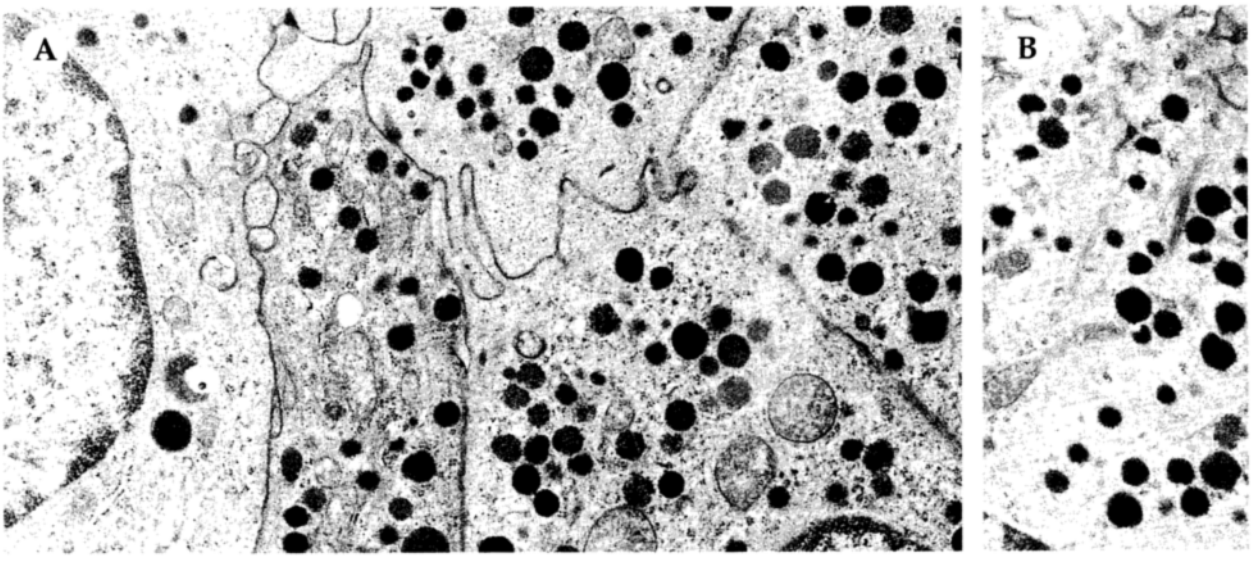

Figure 4. *Ultrastructure of the tumor cells. Detection of (A) abundant neuroendocrine granules with different degrees of density, and (B) intermediate filaments arranged in bundles – (A) x12000, (B) x13000*

Table 1. **Primary antibodies used in this study**

Antibody against	*Type*	*Dilution*	*Source*
Cytokeratin (Kl 1, AE 1 and 3)	monoclonal	1:50, undiluted	Immunotech, Camon
Vimentin	monoclonal	undiluted	Camon
Chromogranin A	monoclonal	undiluted	Camon
NSE	monoclonal	undiluted	Camon
Serotonin	monoclonal	1:10	DAKO
Glucagon	polyclonal	undiluted	BioGenex
VIP	monoclonal	undiluted	BioGenex
Somatostatin	monoclonal	undiluted	BioGenex
PP	monoclonal	undiluted	Eurodiagnostica
Protein S-100	monoclonal	1:100	DAKO
Neurofilaments	monoclonal	undiluted	Camon

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 amphicrine cell type.

In conclusion, the results we present herein are in line with the findings of Faverly et al[4] and support the idea that carcinoid tumors of the middle ear derive from a pluripotent uncommited stem cell with biphasic differential capability.

Literature

1. *Azzoni C, Bonato M, D'Adda T, et al:* Well-differentiated endocrine tumours of the middle ear and of the hindgut have immunocytochemical and ultrastructural features in common. Virchows Arch 426:411-418, 1995.
2. *Davies JE, Semeraro D, Knight LC, et al:* Middle ear neoplasms showing adenomatous and neuroendocrine components. J Laryngol Otol 103:404-407, 1989.
3. *El-Naggar AK, Pflatz M, Ordonez NG, et al:* Tumors of the middle ear and endolymphatic sac. Pathol Annual 29 (Part 2):199-231, 1994.
4. *Faverly DRGS, Manni JJ, Smedts F, et al:* Adeno-carcinoid or amphicrine tumors of the middle ear a new entity? Path Res Pract 188:162-171, 1992.
5. *Hale RJ, McMahon RFT, Whittaker JS:* Middle ear adenoma: Tumour of mixed mucinous and neurocrine differentiation. J Clin Pathol 44:652-654, 1991.
6. *Himi T, Saitoh H, Ohguro S, et al:* Carcinoid of the middle ear and mastoid. Auris Nasus Larynx 22:128-133, 1995.
7. *Hosoda S, Tateno H, Inoue HK, et al:* Carcinoid tumor of the middle ear containing serotonin and multiple peptide hormones. Acta Pathol Japon 42:614-620, 1992.
8. *Krouse JH, Nadol JB, Goodman ML:* Carcinoid tumors of the middle ear. Ann Otol Rhinol Laryngol 99:547-552, 1990.
9. *Latif MA, Madders DJ, Barton RPE, et al:* Carcinoid of the middle ear associated with systemic symptoms. J Laryng Otol 101:480-486, 1987.
10. *Lim DJ, Birck H:* Ultrastructural pathology of the middle ear mucosa in serous otitis media. Ann Otol Rhinol Laryngol 80:838-853, 1971.
11. *Lloyd RV, Sisson JC, Shapiro B, et al:* Immunohistochemical localization of epinephrine, norepinephrine, catecholamine-synthezising enzymes, and Chromogranin in neuroendocrine cells and tumors. Am J Pathol 125:45-54, 1986.
12. *Mandigers CMPW, van Gils APG, Derksen J, et al:* Carcinoid tumor of the jugulotympanic region. 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 118:1341-1347, 1992.
14. *Maschek H, Schrader B, Werner M, et al:* Karzinoid des Mittelohres: Seltener Tumor mit biphasischer Differenzierung. HNO 40:405-409, 1992.
15. *McNutt MA, Bolen JW:* Adenomatous tumor of the middle ear. An ultrastructural and immuncytochemical study. Am J Clin Pathol 84:541-547, 1985.
16. *Murphy GF, Pilch BZ, Dickersin GR, et al:* Carcinoid tumour of the middle ear. Am J Clin Pathol 73:816-823, 1980.
17. *Nakajima T, Watanabe S, Sato Y et al:* An immunoperoxidase study of S-100 protein distribution in normal and neoplastic tissues. Am J Surg Pathol 73:816-823, 1982.
18. *Ruck P, Pfisterer EM, Kaiserling E:* Carcinoid tumour of the middle ear: A morphological and immunohistochemical study with comments on histogenesis and differential diagnosis. Path Res Pract 185:496-503, 1989.
19. *Ruck P, Pfisterer EM, Kaiserling E:* Karzinoidtumor des Mittelohres. Laryngorhinootologie 69:74-76, 1990.
20. *Sakurai M, Mori N, Horiuchi O, et al:* Carcinoid tumor of the middle ear: an immunohistochemical and electronmicroscopic study: report of a case. Acta Pathol Japon 38:1453-1460, 1988.
21. *Stanley MW, Horwitz CA, Levinson RM, et al:* Carcinoid tumours of the middle ear. Am J Clin Pathol 87:592-600, 1987.
22. *Wiedemann B, Waldherr R, Buhr H, et al:* Identification of gastroenteropancreatic neuroendocrine cells in normal and neoplastic human tissue with antibodies against synaptophysin, chromogranin A, secretogranin I (chromogranin B), and secretogranin II. Gastroenterology 95:1364-1374, 1988.