case report

Middle-ear carcinoid tumor with distant metastasis and fatal outcome

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The term carcinoid, karzinoid (carcinoma-like), was first mentioned in the literature in 1907 by Oberndorfer. Since its recognition as a distinct entity it has been quite a controversial tumor, especially with respect to its biological behavior. In fact, although traditionally considered a benign neoplasm, distant metastases and tumor-related deaths were very soon sporadically recorded. 1

Carcinoids are exceedingly rare neoplasms in the middle ear2 and are usually referred to as adenoma/ carcinoid tumors because they are considered benign gland-forming neoplasms with an overt tendency to develop neuroendocrine and mucinous differentiations.3,4

Most literature reviews and textbooks on pathology highlight the benign clinical course of this entity. Some authors, however, have reported in recent years both local recurrences and extracranial lymph node metastases in the neck.5,6 Interestingly, no visceral metastases have been reported so far.9 The case reported here represents a unique example of middle ear carcinoid with regional lymph node and liver metastasis that led to the patient’s death after 11 years of follow up.

CASE

A right middle ear tumor was discovered on otoscopy in 45-year-old man who consulted for hypoacusis. On physical examination, the tumor occupied mainly the middle ear, but extended to the external auditory channel. CT scans showed an increased density in the middle ear that was initially interpreted as cholesteatoma.

A tympanoplastia was performed and the obtained material was diagnosed as middle ear adenoma/carcinoid tumor with positive surgical margins. The patient was then treated with radiotherapy.

Three years later, the patient consulted for otorrhrea, otalgia, hypoacusis, and blockage of the temporomandibular joint. A retrotympanic mass was seen on otoscopy. CT scan showed a middle ear tumor eroding the cranial bone (Figure 1A). The tumor was surgically excised. Five years later, the tumor again recurred. MRI showed the middle ear mass destroying the temporal petrous bone with intracranial extension (Figure 1B). Temporo-parietal craniotomy with partial tumor resection and radiotherapy was performed.

One year later, the patient remained symptomatic and was sent for consultation to another institution. Lymph node metastases were detected on CT scans (Figure 1C). A right petrosectomy and regional lymphadenectomy were performed there. The same histopathological diagnosis was made at that time.

One year later, the patient consulted again in our institution because of a new tumor recurrence. MRI showed a 12 cm in diameter tumor mass at the region invading the medium cranial fossa with compressive signs into the adjacent cerebral tissue. Octreotide-In111 gammagraphy and a CT scan (Figure 1D) additionally revealed liver metastases which were histologically confirmed with core biopsy. The patient then received chemotherapy with carboplatin plus VP16, but died of the disease 5 months later. The evolution since the initial diagnosis to death was 11 years.

Pathological findings

Grossly, the specimens at the first resection consisted of multiple and irregular fragments of hemorrhagic tumor tissue (Figure 2). Subsequent surgical procedures in our institution also included bone and cerebral tissue. Of note, the primary tumor, all recurrences, the lymph node metastasis, and the liver mass all showed the same basic histology. Tumour cells were arranged in nests, ribbons, cords, and acini lying in a fibrous vascular-rich stroma, and showed a monotonous appearance with polygonal shape, eosinophilic granular cytoplasm, and regular nuclei without nucleoli (Figures 3A, 3B). The successive recurrences and metastases did not display significant changes in the tumor morphology. Atypia, mitoses,
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Figure 1. (A) CT scan showing a tumor occluding the external auditory channel and occupying the middle ear. (B) CT scan showing the intracranial tumor extension. (C) CT scan showing a nodal tumor mass in the neck. (D) CT scan demonstrating liver metastasis.

Figure 2. Macroscopic view of the tumor specimens showing irregular hemorrhagic fragments.

Figure 3. (A) Microscopic view of the tumor showing two components, endocrine and adenomatous, lying in a hemorrhagic stroma (H&E ×100). (B) Microscopic detail of the endocrine-appearing area with cords and ribbons of deep eosinophilic cells with no atypia nor mitosis (H&E ×250). (C) Focal intense immunostaining with chromogranin A in the tumor cells (chromogranin A, hematoxylin counterstaining, ×250) (D) Diffuse synaptophysin immunostaining in the tumor cells (synaptophysin, hematoxylin counterstaining, ×250).
necrosis, and angioinvasion were not seen. One of the recurrences showed direct invasion into the cerebral tissue. The lymph node metastasis displayed extracapsular extension of the tumor. The tumor cells showed positive immunostaining with chromogranin (Figure 3C), synaptophysin (Figure 3D) and CD56 in many areas. Ki67 showed nuclear positivity in <20% of tumor cells.

**DISCUSSION**

The carcinoid tumor was first described in the middle ear by Murphy et al in 1980\(^9\) and ever since experts in the field have been engaged in a permanent debate: do this tumor and the previously described middle ear adenoma\(^7\) represent the same entity? The current WHO classification,\(^2\) a recent review of these tumors,\(^4\) and the hitherto largest published series\(^3\) all favor the opinion that the adenoma and carcinoid tumor in the middle ear represent two faces of the same coin. The synonymy of various terms has contributed to the confusion. Torske and Thompson\(^3\) proposed the term neuroendocrine adenoma of the middle ear in their series of 48 cases, and Michaels and Soucek,\(^4\) in the 2005 WHO classification edition, defined this tumor as a benign glandular neoplasm with a variable tendency towards neuroendocrine and mucous differentiations. They accepted adenomatoid tumor, neuroendocrine adenoma, and middle ear carcinoid as synonyms. When compared with other head and neck territories, i.e. the larynx, the confusion still remains. Here, carcinoid tumor, atypical carcinoid tumor, and poorly differentiated neuroendocrine carcinoma are related entities with very different clinical behavior that are distinguished exclusively on the basis of their histological characteristics.

Wherever they arise, carcinoid tumors are well-defined neoplasms. They show very few if any nucleoli, very scarce (less than 2/10 HPF) or no mitosis, and no necrosis, nuclear pleomorphism, nor angioinvasion. Despite the fact that all carcinoids share a common histology, the clinical behavior is quite different and depends, for example, on the primary site of origin.

Middle ear carcinoids usually pursue an indolent clinical course. However, local recurrences and regional lymph node metastases have occasionally been reported. Mooney et al,\(^5\) Menezes and Wakely,\(^6\) and Pellini et al\(^7\) all reported isolated cases of middle ear carcinoid tumor with recurrences and loco-regional lymph node metastases. The AFIP series reports 8 recurrences after surgery in a total of 48 patients (16.6%), but no tumor-related death.\(^3\) Ramsey et al,\(^9\) in a recent paper adding 4 cases to a literature review, identify a total of 22% of local recurrences and 9% of regional lymph node metastases. Michaels and Soucek mention in the last WHO book on head and neck tumors that “there have been a few recurrences after incomplete local surgical resection”.\(^4\)

Finally, Ferlito et al\(^9\) claim to consider this entity as a low-grade and slow growing tumor with some capacity for regional lymphatic dissemination. In addition, they specifically state that “to date, distant metastases have not been associated with middle ear carcinoid tumors”.\(^9\)

Laryngeal carcinoids, however, behave much more aggressively, with 33% of the reported cases developing distant metastases to the liver and bone.\(^11\) A critical review applying strict histological criteria probably would reclassify some of them as atypical carcinoids.\(^12\) In addition, Soga et al\(^14\) emphasized the unpredictability of its biological behavior.

Apart from the presence of adjacent tissue invasion or metastases, there are no reliable markers for evaluating the biological aggressiveness of these neuroendocrine neoplasms.\(^13\) A proliferative index >2% (Ki67) may predict the malignant potential, but immunostaining is usually focal and may not appear in the first diagnostic biopsy. On the other hand, it is difficult to apply the histological criteria of laryngeal atypical carcinoid to middle ear carcinoid tumor because this entity has not yet been described in this topography.\(^4\)

The diagnosis of carcinoid tumor relies on the identification of conventional neuroendocrine markers in an otherwise histologically typical tumor. A multihormonal production capacity has been described in these cases.\(^16\) The differential diagnosis includes paragangliomas, negative with cytokeratins; ceruminomas, a double cell layer with apocrine changes in luminal cells, and Schneiderian-type papillary tumors of the region. A metastatic seed from carcinoid tumors of the gut or even an amelanotic melanoma should also been ruled out.\(^17\)

To conclude, we report the first documented case of middle ear carcinoid tumor with distant metastases and tumor-related death after 11 years of follow up. Despite these rare tumors having been considered to date as low aggressive neoplasms, we advise a long-term follow up to ascertain its supposed benignity. The term atypical carcinoid tumor could be applied in these specific cases with proven aggressive behavior. We propose in these tumors the adoption of the same grading system based in mitotic index and Ki-67 index recently applied to foregut neuroendocrine tumors.\(^18\)
REFERENCES