Carcinoid Tumor of the Jugulo-Tympanic Region

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Increased levels of 5-hydroxyindole acetic acid (5-HIAA) were found in a patient with a tumor arising in the middle ear. Iodine-123-metaiodobenzylguanidine ([^{123}I]MIBG) scintigraphy and biochemical analysis showed evidence of serotonin production by the tumor. Immunohistochemistry of the tumor showed reactivity with antibodies directed against serotonin, chromogranin, leu-7 and neuron-specific enolase; S-100, *met*-enkephalin, leu-enkephalin and glial fibrillary acid protein were negative. This case suggests a close relationship between functioning paragangliomas and carcinoid tumors because a strong clinical and endocrinological resemblance exists. The hormonal activity found is discussed in relation to extra-adrenal paragangliomas. We recommend urinary screening not only for detection of increased levels of catecholamines, but also of 5-HIAA in all patients with paragangliomas of the head and neck. When elevated levels are found, [^{123}I]MIBG scintigraphy should be performed to localize the areas of increased uptake in or outside the head and neck region.

Key Words: carcinoid tumor; 5-hydroxyindole acetic acid; iodine-123 MIBG; paragangliomas; serotonin; catecholamine

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Paragangliomas of the head and neck are rare tumors. Together with aortico-sympathetic paragangliomas and adrenal pheochromocytomas they can be classified as paragangliomas (*1*). Clinically detectable endocrine activity by these tumors is thought to occur only in a small percentage of head and neck paragangliomas; almost all cases reported to be hormonally active show secretion of norepinephrine. Occasionally, secretion of dopamine has been reported (*2*).

We previously reported [^{123}I]MIBG uptake of paraganglioma of the head and neck region to be usually low-to-moderate (*3*). We also studied a patient with a carcinoid tumor of the jugulo-tympanic region that showed high [^{123}I]MIBG uptake. This tumor produced serotonin clinically and immunohistochemically. In this report, we discuss the relationship between carcinoid tumors and paraganglioma, as well as the role of [^{123}I]MIBG scintigraphy in the diagnosis of these tumors.

CASE REPORT

A 64-yr-old man presented with a 6-mo history of malaise and pain in both the left ear and left temporal region. He had lost 5 kg weight during the past 6 mo but was otherwise asymptomatic. The patient had no otorrhoea or tinnitus, nor did he have flush attacks, palpitations, dizziness, blocked nose or diarrhea.

His medical history revealed an appendectomy 30 yr before and a left-sided chronic otitis media 20 yr ago that was treated conservatively and surgically by left atticoantrotomy. Fifteen years later, left conservative radical mastoidectomy was performed and a revision left radical mastoidectomy was necessary 3 yr before the current presentation. Since this last operation, hearing in the left ear was lost. Five years ago, a middle-ear biopsy revealed tumorous material histologically classified in the referring hospital as probably compatible with a paraganglioma. There was no family history of paragangliomas.

Physical examination at presentation revealed a 4 × 2 cm immobile painless swelling near the left proximal sternocleidomastoideal muscle. There were no neurological symptoms except loss of ability to calculate. Endocrinological analysis revealed normal urinary excretion of free catecholamines (epinephrine 0.04 μmole/24 hr, norepinephrine 0.37 μmole/24 hr and dopamine 1.21 μmole/24 hr). Urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) (299 μmole/24 hr) was far beyond the reference range (10–42 μmole/24 hr). After subcutaneous administration of 3 times 100 μmole somatostatin in one day, a decrease was noted in the next four sequential days of urinary 5-HIAA excretion (117, 125, 115, and 100 μmole/24 hr, respectively).

CT of the head performed with intravenous contrast infusion revealed a large mass of 10 × 9 × 8 cm at the level of the skull base with extension into the middle and posterior fossa with bony destruction of the floor of the middle fossa and the petrosal bone. MRI demarcated the tumor even more clearly with marked enhancement after intravenous injection of gadopentetate. The tumor showed the serpiginous flow void phenomenon (Fig. 1A–C), as described for paragangliomas (*4*).

Total-body scintigraphy was performed after intravenous injection of 370 MBq [^{123}I]MIBG (specific activity at least 925 MBq/mg). Immediately after injection, 10 flow images of the head and neck were obtained at 15-sec intervals. At 24 and 48 hr postinjection, anterior and posterior images of the total body and four images of the head and neck were obtained with a large field of view gamma camera equipped with a low-energy, general-purpose collimator and interfaced to a dedicated computer. SPECT imaging was not performed. The tumor showed high vascularity on the flow images (Fig. 2A) and high radiotracer uptake on the images obtained after 24 and 48 hr (Fig. 2B) in the left middle and posterior cerebral fossa, which corresponded to the location of the tumor on CT and MRI. No other sites with abnormal [^{123}I]MIBG uptake were demonstrated. MIBG uptake by the tumor was 2.1% of the administered dose. A bone scan did not show any skeletal metastases. CT and MRI of chest and abdomen did not reveal signs of metastases either.

A new biopsy of the tumor was performed. A microscopic examination (Fig. 3) showed features similar to the previous biopsy. The tumor had a solid appearance composed of interlacing cell nests. These epithelial nests were separated by an avascular fibrous stroma. The cells showed a uniform appearance with an elliptical shape and a polarized, eccentrically located nucleus towards the fibrovascular margin of the cell nests. The cytoplasm had a granular appearance. No cell embracing or vascular cytoplasmic changes were observed. No zellballen formations were observed. Mucin stains were negative. Staining with grimelius silver-stain and diazonium salts revealed positivity in all cells and a bright fluorescence was observed after using ultraviolet light.

Immunohistochemistry revealed a clear positive reaction with antibodies directed against chromogranin, synaptophysin, neuron-

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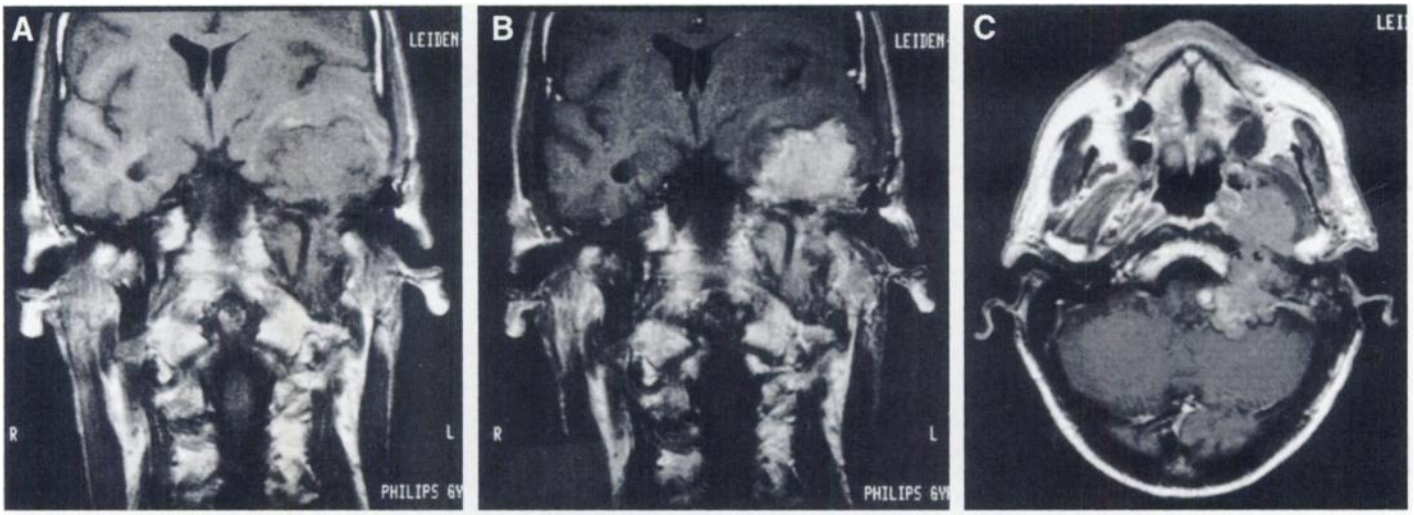

FIGURE 1. Coronal T1-weighted image (SE TR 600/TE 20) shows a large tumor in the left temporal region encasing a left carotid artery with some flow voids (A). Coronal T1-weighted image (SE TR 600/TE 20) after intravenous injection of gadopentetate dimeglumine demonstrates strong enhancement of the mass (B). Transverse T1-weighted image (SE TR 600/TE 20) after intravenous injection of gadopentetate dimeglumine better shows intracranial and extracranial extension of the tumor (C).

specific-enolase, serotonin and leu-7. Antibodies directed against nongranule-dependent protein (PGP 9.5) showed weak focal staining only. Staining for S-100, leu-enkephalin, met-enkephalin, glial fibrillary acidic protein and neurofilaments showed no reactivity. In view of these features, the tumor was diagnosed as a carcinoid tumor of the middle ear.

During subsequent follow-up, the tumor showed rapidly expansive growth. Because of the tumor's troublesome location, treatment was started with 7.2 GBq [^{131}I]MIBG infused intravenously over 1 hr. This dose was repeated after 2 mo. During subsequent follow-up, 5 HIAA excretion did not change substantially. Post-therapy [^{123}I]MIBG scintigraphy was not performed. No objective regression of the tumor was observed on MR images, and despite additional endovascular embolization and tumor debulking, the patient deteriorated and died 2 yr later. An autopsy was not performed.

DISCUSSION

Paragangliomas of the head and neck secreting catecholamines and clinically presenting as pheochromocytomas are well-known but are considered to be uncommon. The percentage is assumed to be about 1% of all paragangliomas (*5*). This figure probably underestimates the real prevalence since an increased awareness of the possible hormonal activity and better diagnostic methods have resulted in a steadily growing number of reported cases. These were almost all associated with excessive production of epinephrine and norepinephrine, whereas in the remaining cases dopamine was the hormone predominantly produced (*2*).

We found two other reports in the literature on paraganglioma producing a carcinoid syndrome. In 1974, Pearse reported a carcinoid APUD-oma arising in a carotid body paraganglioma (*6*), and in 1980 Farrior et al. described a patient with a carcinoid syndrome caused by a jugulo-tympanic paraganglioma (*7*). This patient became aware of his symptoms only after the tumor had been found to be a carcinoid tumor after pathological examination and he had been asked thoroughly about the presence of typical complaints. The abnormal production of serotonin was never assessed in either case. Considering the differential diagnosis with a paraganglioma, several histological observations are important. Both tumors may show neuroendocrine activity and argyrophilia, and endocrine activity is reported in paragangliomas as well.

In our case, the absence of the zellballen pattern, or an extensive microvascular network, characteristic of paragangliomas was observed. Moreover, our case showed immunohistochemical reactivity with the leu-7 antigen, a feature which is unusual in paragangliomas and well-known in carcinoid tumors. This tumor was thus immunohistochemically negative for neurofilaments, whereas paragangliomas are usually positive. A S-100-positive network of sustentacular cells was not observed either.

Our patient lacked the typical complaints, but the elevated urinary excretion of 5-HIAA in combination with extremely high uptake of MIBG and the histological features of the tumor clearly warrant the diagnosis of a hormonal active carcinoid tumor.

This case displays several interesting aspects. It illustrates that tumors of the head and neck can be hormonally active, which suggests a pheochromocytoma or a carcinoid tumor elsewhere in the body. Several patients with functioning paragangliomas have died from uncontrollable hypertension during or after surgery. Consequently, a preoperative examination for these tumors should include urinary analysis to detect excessive secretion of catecholamine and 5-HIAA. Iodine-123-MIBG scintigraphy should be performed to localize the source of hormone production, to exclude other concurrent functioning tumors or metastases, to characterize the tumor functionality and to explore the possibility of [^{131}I]MIBG therapy. MIBG has a high sensitivity for functioning paragangliomas and moderate sensitivity for carcinoid tumors (*3,4,8,9*).

In 1974, Bolande hypothesized that paragangliomas and carcinoid tumors were related since both are derived from neural crest cells (*10*). Lawson found that paragangliomas also contain granules composed of serotonin, besides catecholamine storing granules in 1980 (*5*). Our case, like others (*11–15*), provides further support for this concept and emphasizes the close relationship between these two types of tumors.

Several cases of carcinoid tumors in the middle ear have been reported (*13,16–24*). All of these tumors were small and confined to the tympanic cavity, and none of these patients showed increased 5-HIAA excretion nor bony destruction of the petrous bone (*7,16–25*). No logical explanation could be given for this unusual localization. Although the case described by Farrior et al. and our case differ clearly from other cases by tumor size, bony destruction and hormonal activity, we hypothesize that these carcinoid tumors may also arise from paragan-

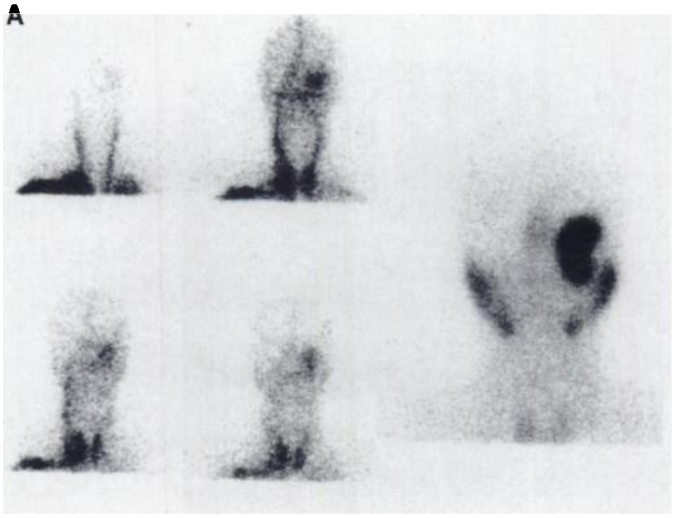

FIGURE 2. Four early images taken 1 min postinjection of 370 MBq [^{123}I]MIBG with a 15-sec interval illustrate high tumor vascularity. Anterior view of the head at 24 hr shows high uptake of [^{123}I]MIBG (A). Whole-body images 24 hr after injection do not show any other site of abnormal MIBG uptake (B).

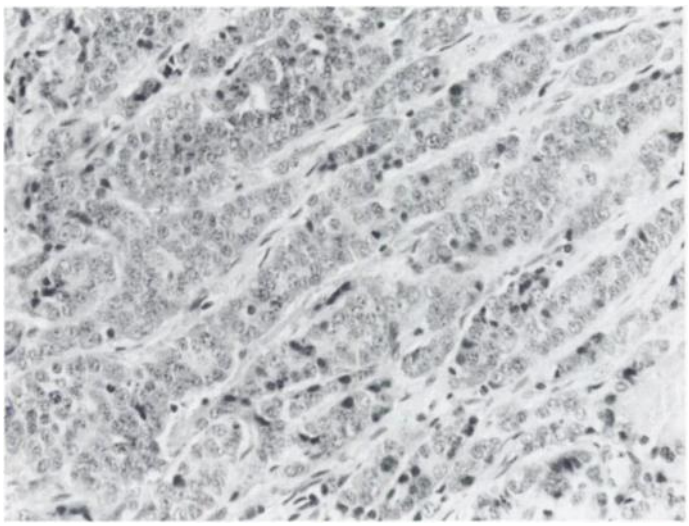

FIGURE 3. Light-micrograph of the carcinoid tumor of the middle ear. Note the nest-like appearance of the cells with polarized nuclei towards the fibro-vascular stroma (H&E 40×).

glioma-like tissue situated in the middle ear or more specifically, from the glomus tympanicum. Perhaps there is not always an absolute distinction, but rather, a subtle transition between a paraganglioma and an (atypical) carcinoid tumor.

Surgery should be the first choice treatment of these tumors, but high doses of radiotherapy (29–52 gray) (*26*), [^{131}I]MIBG (*3,27*) and somatostatin might be beneficial.

CONCLUSION

We present a patient with an exceptional jugulo-tympanic tumor, in whom the diagnosis of a carcinoid tumor was made based on urinary levels of 5-HIAA, [^{123}I]MIBG scintigraphy and histopathology.

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