PARAGANGLIOMA

Light and Electron Microscopic Study

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SUMMARY: *Paraganglioma:* Histological. (24 cases) and ultrastructural (3 cases) findings of paraganglioma have been analised. Organoid structures (Zellballon) and the peresence of argyrophil granules with Grimelius procedure were the most important findings leading to diagnosis, by light microscopy and electrone dense granules by electron microscopy. The precent study showed the presence of supporting cells, in some cases suporting cells were located at the periphery of single or groups of chief cells, especially in places were the Zellballon were well organised. The chief cells were interconnected to each other and in some places to the cytoplasmic proceases of the supporting cells by desmosomelike structures.

INTRODUCTION

Paraganglioma is a rare tumor. Paraganglionic cells are derived from the neural crest and cells of mesodermal origin contribute to the structure of paraganglionic bodies[1]. The tumor arising from these bodies, is named "chemodetoma" because of its similarity to carotid body structure and chemoreceptor function.[2-3] These tumors are also referred by different names: "non-chromaffin paraganglioma[4]", "paraganglioma" referring to its location such as carotid body paraganglioma, "apudoma", "neurolophoma"[5] or "neurochristoma."[6]

MATERIALS AND METHODS

Twenty four cases were routinely processed for paraffin embeding and stained with hematoxyline and eosin. Only 6 cases were stained with PAS, PAS-orange G, Masson-trichrome, Masson-Fontana for argentaffin, Gomori and Grimelius for argyrophil reactions.

The specimens obtained for electron microscopy in 3 paraganglioma cases were fixed in buffered-formaldehyde and then overnight in the buffered solution at PH 7.2. The material was post-fixed in % 1 osmium tetroxide[7] and then dehydrated in solutions of acetone and embedded in vestropal-W. One micron thick sections were cut and stained with methylene blue and representative tissue areas were selected by light microscope. Ultrathin sections were cut and stained with uranyl acetate and lead citrate for electron microscopy (Philips 301).

FINDINGS

The tumors ranged in size from 1 cm. up to 10 cm. in 23 cases. Only in one case, the tumor was larger than the others. The tumor derived from th carotid body in 15 cases, from the jugular body in 7 and from the retroperitoneum in 2 cases (Tablo 1).

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Table 1: Presentation of 24 paragangliomas

Number	Prot No.	Age,Sex	Location	Duration (year)	Macroscopy	Microscopy
1)	309/35	33,F	Neck, L	1	6x5 cm. soft pink-yellow	Organoid pattern with two types of cells.
2)	488/40 (necropsy)	55,M	In the anterior area of Aorta Abdominalis			
3)	a- 567/45 b- 585/45	43, M	Neck with metases to the liver	2	15x10 cm.	Organoid pattern central necrosis cal cification
4)	1287/53	29, F	External canal and antrum		2x1 cm. yellowish	Organoid pattern small cells and trabeculae.
5)	3602/53	70, F	Neck, R	8 with recurrence	5x4 cm. pink soft	Organoid pattern with epithelioid and fusiform cell, fibrous areas.
6)	2279/54	55,F	Neck	-	8x4 cm.	Organoid pattern with light and dark cells giant nucleoli vessels.
7)	4527/61	30,F	Middle, ear,L	-	1 cm. darkred	Organoid pattern with acidophilic granules, giant nucleoli.
8)	1047/63	50,F	Ear canal, L	-	1x0.5 cm.	Epithelioid cells with acidophilic granules, vessels.
9)	1373/64	36,F	Neck, L	-	8x4 cm. grayish	Organoid pattern, epithelioid cells with acidophilic granules.
10)	4183/64	48,M	Neck	-	25 cm. pink	Organoid pattern, Epithelioid cells with acidophilic granules, hyalinized areas.
11)	6396/64	56,M	Neck, L	-	2 cm.	Organoid pattern. Epithelioid cells with acidophilic granules.
12)	4774/65	48,M	Neck	-	4x3x2 cm. gray-yellow	Small organoid pattern with dark and epithelioid cells.
13)	6435/65	40,F	Middle ear	-	0.5 cm.	Organoid pattern with small dark cells.

14)	1084/66	50,M	Neck,metastasized to cervical lymph nodes	-	3x2x1 cm.	Organoid pattern with dark with dark cells.
15)	2834/67	38,M	Middle ear,L	-	3 mm. pink	Organoid pattern with small cells.
16)	1724/70	56,F	Middle ear	-	4 mm.	Organoid pattern with small cells.
17)	4172/72	50,M	Neck,R	-	4x3x2 cm. gray encapsulated.	Organoid pattern with epitlioid cells, giant nucleoli vessels.
18)	5702/72	45,M	Neck,L	——	5x4x1 cm. red soft	Organoid pattern with light cells, trabeculae, giant nucleoli vessels.
19)	5605/73	26,F	Neck, L	-	4 cm. gray-white,	Organoid pattern with light and dark cells, vessels.
20)	11285/80	45,F	Middle ear,L	-	1x0,6 cm. pink	Organoid pattern with small cells, angiomatous and hyalinized areas.
21)	2967/81	50,F	Submandibular	-	2.5x2x1 cm. pink-read	Organoid pattern with light and dark cells, giant and multiple nucleoli.
22)	a- 4980/81	47,F	Retroperitoneal metastasized to paraaortic and to cervical lymph nodes	-	2.5x2 cm. soft	Organoid pattern with light and dark cells, necrosis, giant cells.
23)	10132/81	48,F	Submandibular,L	-	3x2x1 cm. pink encapsulated.	Organoid pattern with small epithelioid cells.
24)	12579/81	27,M	A.carotis communis	-	6x5x3 cm. pink encapsulated,firm.	Organoid pattern with small epithelioid cells

The tumor was present for 8 years in one case and for 2 years in the other which had recurred. Malignant paraganglioma was diagnosed in 3 cases (case no.: 3,14,22). The tumor originated from the retroperitoneum, metastasized both to the retroperitoneal and cervical lymph nodes. Two paragangliomas were located in the cervical area, in the former was noted a metastasis to the cervical lymph nodes, in the latter to the liver.

Fourteen cases were females, 10 males. The ages ranged from 20 to 70. The tumor was mostly encountered in the 5-6 th decades (Table 1).

Light Microscopic Findings: The tumor consisted of an organoid pattern (Zellballen), which was surrounded by argyrophil fibers (Fig: 1). The reticulin

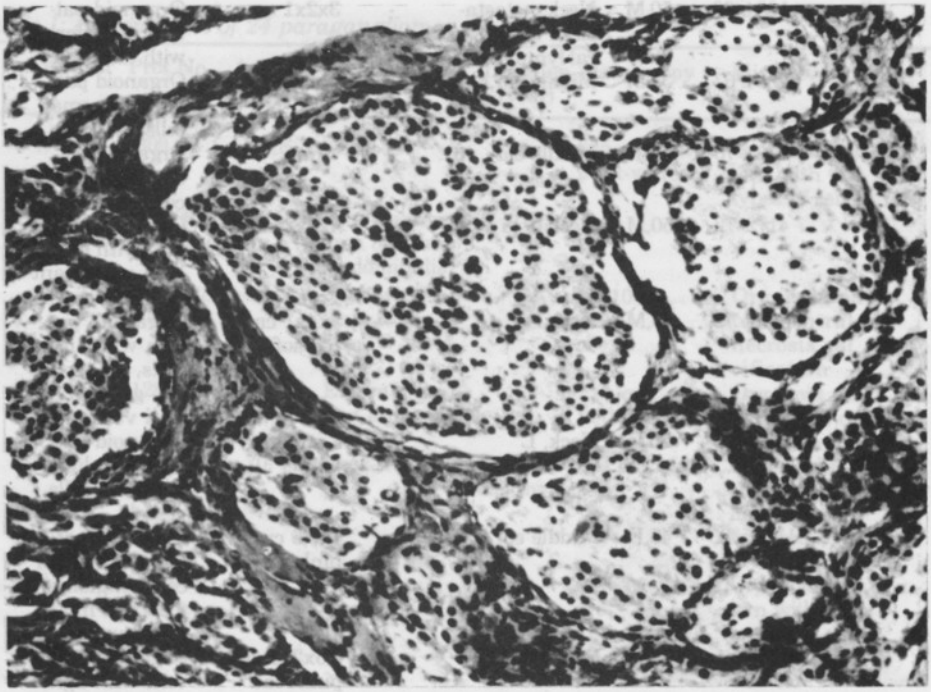

Fig 1: Organoid (Zellballen) pattern in paraganglioma (Hematoxylin eosin stain. Case No. 5605/73, X 120).

fibers did not surround the individual tumor cells. In some areas alveolar pattern, anastomosing cords, pseudorosettes, pseudo-acinar pattern, concentric structures or interlacing fascicules, giving pseudocarcomatous appearance, were seen.

The tumor consisted of light and dark cells. The tumor cells were ovoid, polyhedral or epithelioid in shape. In some areas, where pseudosarcomatous pattern was seen, spindle cells were found. Light cells showed a clear cytoplasm with uniform round acidophilic granules and an epithelioid appearence. The dark cells were oval or spindle-shape, sometimes of syncitial appearance. Their cytoplasm were acidophilic and the cytoplasmic granules were not uniform. These cells were mixed together, but light cells were reduced in number in contrast to dark cells in some areas or vice versa. In some nests light cell clusters surrounded by dark cells. The cellular pleomorphism was obvious.

The blood vessels consisted mostly of anastomosing capillaries and tumor was poor in stroma. The blood vessels were distinct in some areas suggesting an angiomatous tumor. In some places characteristically a hyaline change was conspicuous around the vessels (Fig. 2). The tumor cells were identified as palisadic in shape, in these vascular regions. There was no close relationship between the tumor cells and the vessels.

Malignant paraganglioma cases showed cellular pleomorphism, bizzare giant cells. Necrosis was either extensive or localized in the central areas of the nests.

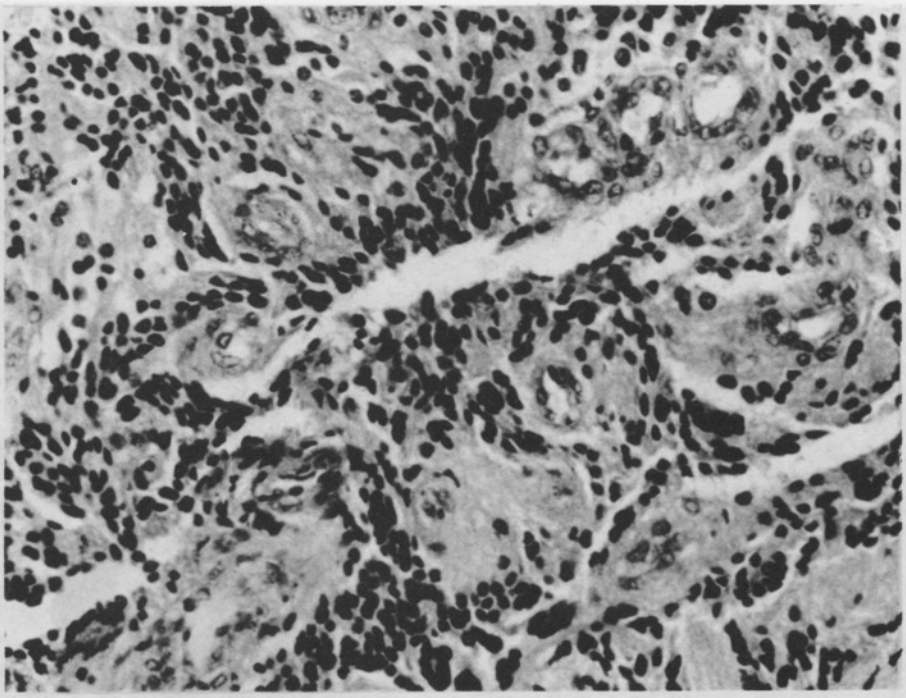

Fig 2: Angiomatous area and syncytial tumor cells in paraganglioma (Hematoxylin-eosin stain. Case No. 6296/81, X 160).

The argentaffin reaction was negative, but argyrophil reaction was positive with Grimelius stain in the cytoplasm of tumor cells. In addition PAS stain was negative, but light red granules were seen with PAS-orange G and Masson trichrome.

Electron microscopic findings: Ultrastructurally two cell types, chief cells and sustentacular or supporting cells were found. The predominant cells were chief cells. The chief cells were light and dark in appearance. The light cells consisted of a large number of round uniform secretory granules (Fig: 3). These granules showed an osmiophilic dense central core surrounded by a clear zone and limited by a fine membrane. These cells showed predominance of the smooth over the rough endoplasmic reticulum. Free ribosomes and mitochondria were sparse. The Golgi apparatus was well developed. The dark cells were characterized by compact organelles, numerous mitochondria, free ribosomes and sectretory granules of varying shape and size. Sometimes mitochondria were tightly packed giving the appearence of oncocytic cells of endocrine tumor (Fig: 4).

The nuclei of the chief cells were small and round and contained one sometimes two prominent nucleoli. The nucleoli consisted of inclusion-like structures imparting the nucleoli "bull's eye" appearence (Fig: 5).

The supporting cells were usually triangular, fusiform or crescent-shaped. Their nuclei were ovoid or lenticular and sometimes irregular. Sustentacular cells

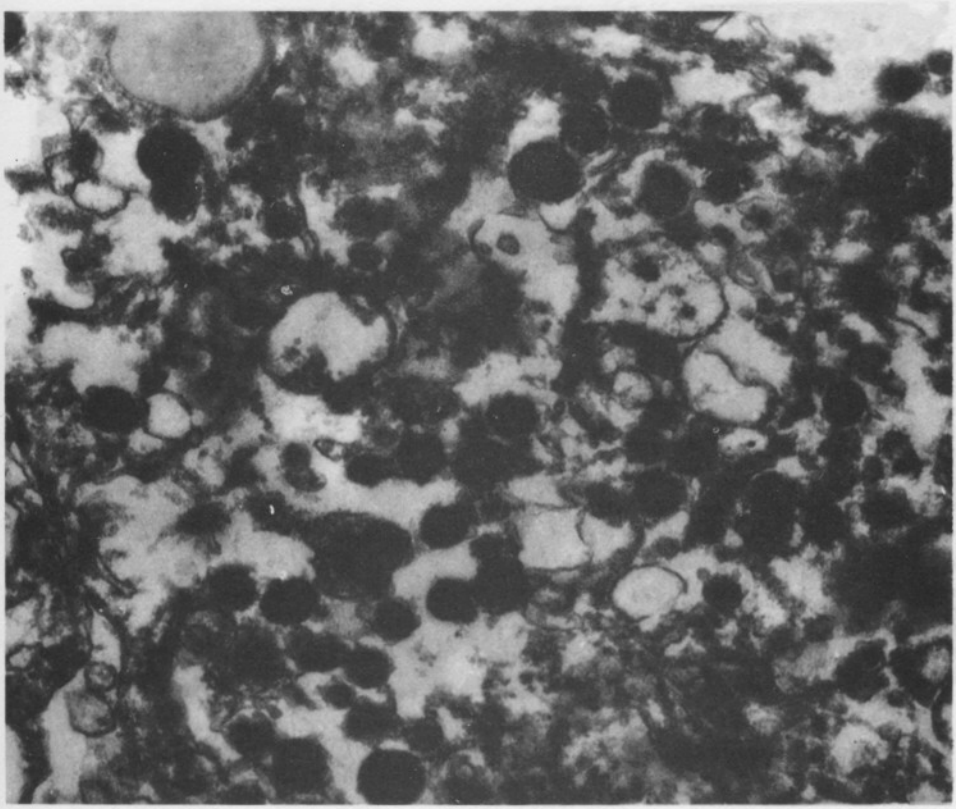

Fig 3: Membrane bound neurosecretory granules in paraganglioma (Case No. 12579/81, E.M X 25.000).

were found in the zellballen at the periphery of chief cells usually in a semilunar fashion (Fig: 6). These cells possessed slender cytoplasmic processes extending between and around the chief cells and chief cell clusters. The cell body and their processes of sustentacular cells enveloped by the basal lamina. The smooth endoplasmic reticulum of sustentacular cells was sparse and in some areas it was arranged in lamellae or whorls. Granular endoplasmic reticulum occasionally was arranged in short tubular and Y-shaped structures.

The chief cells were interconnected to each other and to the cytoplasmic processes of the supporting cells by desmosome-like structures (Fig: 4).

There was no direct relationship between the chief cells and vessels. They were separated from the capillary lumen by endothelium, capillary basement membrane and pericytes or their processes and processes of the sustentacular cells.

DISCUSSION

Tumors of the paraganglionic tissues are most frequently derived from the

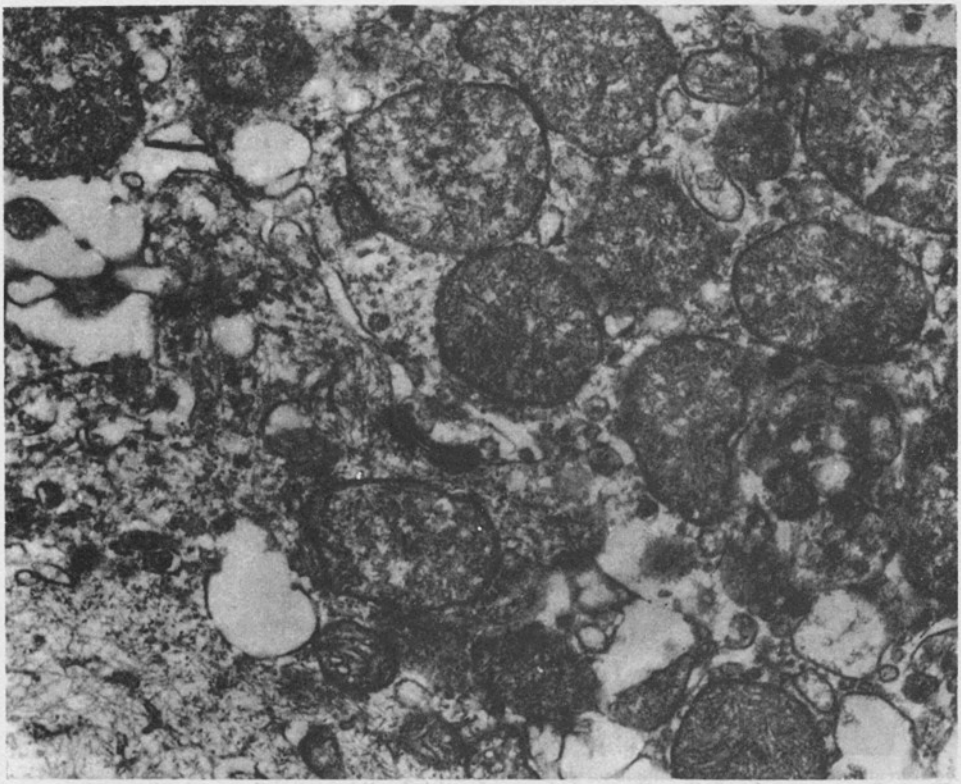

Fig 4: Paraganglioma cells with numerolus mitochondria. Desmosomes between chief cells (Case No. 2967/81, E.M X 19.000).

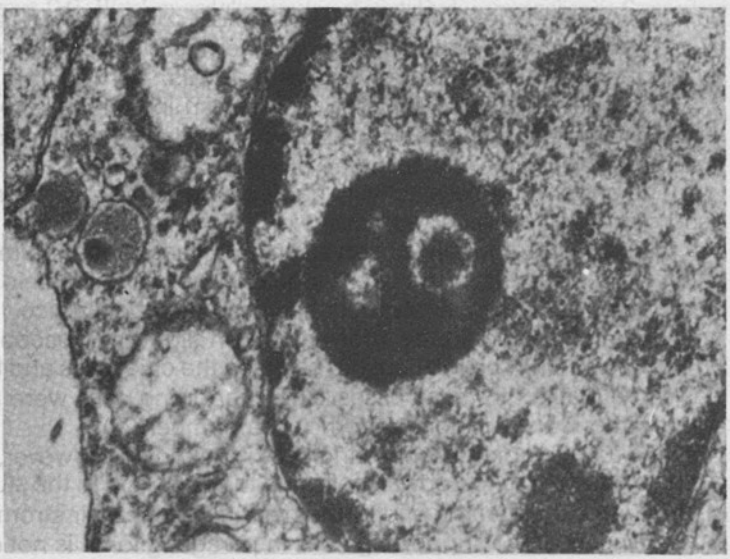

Fig 5: Tumor cell with prominen nucleoli and inclusion-like structure (Case No. 2967/81, E.M X 25.000).

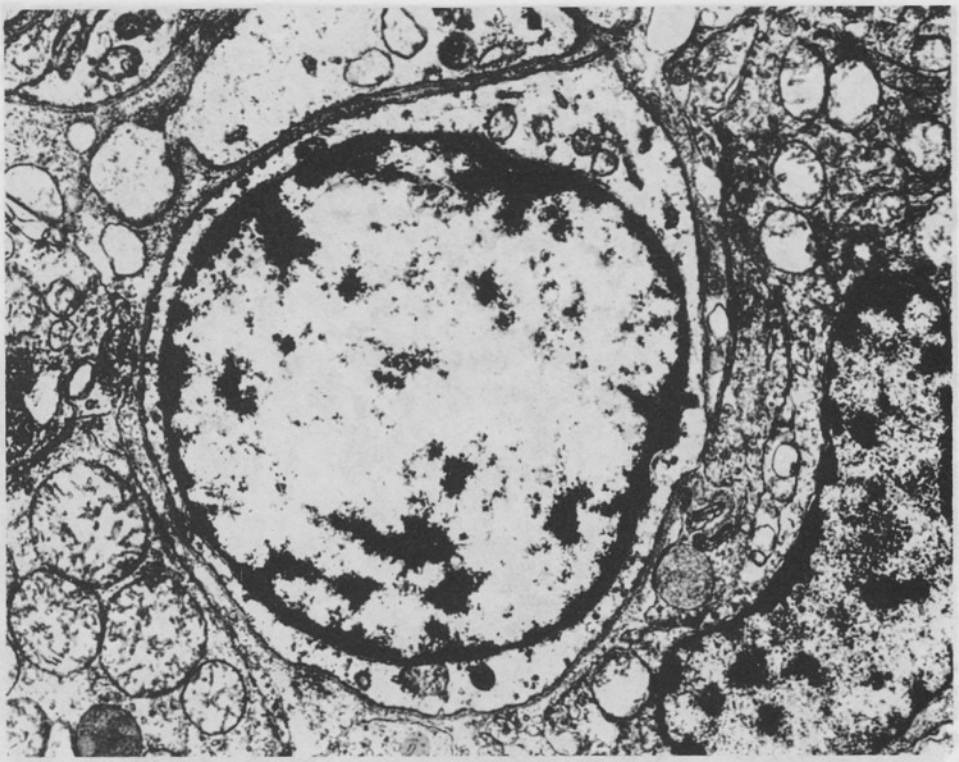

Fig 6: Sustentacular cell at the periphery of a chief cell in a semilunar fashion (Case No. 2967/81, E.M X 7.100).

carotid body and jugular body. They are most common in females, as in our cases.

Ultrastructurally, in the organoid pattern of the tumor are generally noted two types of chief cells with a few supporting cells.

The nuclei in the tumor cells showing an inclusion like pattern[3],[9] are not only related with a nuclear angulation but also this pattern is due to degeneration, because they are seen isolated in nucleoli as we have suggested.

The supporting cells actively participitate in the formation of paraganglioma according to a few reported[10] cases.

We ultrasutructurally observed in two cases (case number 21,23) that the chief cells or their nests were encircled by cytoplasmic processes of the supporting cells, which showed a semilunar appearance. Semi-tihn sections provided some additional information on light microscopic features of the organoid pattern. The relationship between the chief cells and the supporting cells was more distinct in these cases. The supporting cells were not encountered in areas without an organoid pattern (case number 22).

The function of the supporting cells is unknown. However, these cells showed a close relationship to Schwan cells and to glia cells.[10] In the study of Chaudhry[11] et al, the tumor showed the end of the nerve fibers in their stromal component. The exact genesis of the supporting cells in paraganglioma is not clearly understood.

In the diagnosis of the tumor by light microscope, the organoid pattern and neurosecretory granules are very important. Grimelius stain is a specific method for diagnosis of argyrophil neurosecrotory granules.

It is very difficult to decide whether a paraganglioma is malignant or benign, by the histopathological structure. The findings of malignancy for paraganglioma are a central necrosis in Zellballen, vascular invasion and mitosis according to Lack et al.[12] The sign of malignant nature for the tumor is at least the presence of two findings of them. The metastatic spread of the tumor was frequently identified in cases with follow-up[1]. In addition, there is a relation between the location and the ratio of metastasis. If the tumor originated from the retroperitoneum, the ratio of metastasis was 28 %, if from the intravagal 20 %, and if from the carotid body 6 %.[13] In our 3 cases, diagnosis was malignant paraganglioma, the tumors derived from the retroperitoneum and the others arose from the carotid bodies.

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