

A Composite Pheochromocytoma-ganglioneuroma: A Case Report

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Abstract Composite pheochromocytomas are considered rare neoplasms of the adrenal gland. We report a case of composite pheochromocytoma in a 53-year-old woman, with a 4-year medical history of uncontrolled hypertension without hypokalemia and treated with three antihypertensive. A computed tomographic scan was performed, showing the presence of a spontaneously hypodense adrenal mass of 6 x 6 x 3 cm at the expense of the outer arm of the right adrenal gland, and with microcalcifications and a double component. Laboratory studies showed elevated urinary metanephrines. Diagnosis of pheochromocytoma was retained. The patient underwent surgery and pathologic examination concluded the presence of a composite pheochromocytoma.

Keywords: hypertension, hypokalemia, adrenal gland, composite, pheochromocytoma, ganglioneuroma

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1. Introduction

Composite adrenal medullary tumors, composed of both pheochromocytoma and ganglioneuroma, are extremely rare. Histologically, the endocrine component is that of a typical pheochromocytoma, whereas the neuronal component is characterized by mixed areas of ganglioneuroma, neuroblastoma or ganglioneuroblastoma [1,2].

2. Case Report

A 53-year-old woman, with a 4-year medical history of uncontrolled hypertension without hypokalemia and treated with three antihypertensive. She reported a maximum systolic blood pressure reaching 200 mmHg in one occasion. Before the onset of right flank pain, abdominal ultrasound examination was done and showed a lesion of the adrenal gland measuring 46 x30mm, hypoechoic, well-limited.

Furthermore, the patient reclaimed episodes of palpitation and facial flushing. The physical examination was normal, without any skin lesions. Laboratory studies showed elevated urinary metanephrines (8,6 $\mu\text{mol}/24\text{H}$, normal: <5,5 $\mu\text{mol}/24\text{H}$).

Aldosterone, renin, calcium, chromogranin A were within normal limits. Cortisol levels after dexamethasone suppression was inferior to 50 nmol/l.

A computed tomographic scan was performed, showing the presence of a spontaneously hypodense adrenal mass of 6 x 6 x 3 cm at the expense of the outer arm of the right

adrenal gland, with microcalcifications and a double component: one of the components did not change after the injection of a substance of contrast (PDC) while the other component's density was enhanced explosively after the injection of PDC. This mass pushed the left renal vein in front and came in contact with segment I of the liver, the diaphragm and the spine. Diagnosis of pheochromocytoma was retained. The patient was prepared for surgery with the administration of a combination of alpha blocker and beta-blocker, leading to a good balance of the blood pressure. Intra-operative exploration showed a right retroperitoneal mass, independent of the right adrenal gland and of about 6 to 7 cm high, with an extension axis, resembling the aspect of a ganglioneuroma cell. Removal of this mass along with right adrenalectomy were performed without complications. The patient's postoperative course was normal. Hypertension remained controlled with calcium channel blocker.

Pathologic findings in general examination were the following. In formalin, a piece of the removed adrenal gland was received in two fragments; upon examination of the first piece, the first thing we noticed was the appearance of a fleshy and soft fragment measuring 5 x 4 x 2.5 cm, and which looked heterogeneous, grayish in color and somewhat brownish when cut. The second fragment was slender and 8 x 4cm, having an aspect of an adrenal hemorrhagic parenchymal when cut.

Histologically the adrenal tumor was biphasic in aspect, formed by a proliferation of two different contingents in tumor approximately equal in volume, separate from each other by a thick continuous capsule (Figure 1).

The first component consists of a diffuse tumor proliferation made of sheet piles, limited to the stroma

vascular component. Tumor cells were medium to large in size, with finely granular eosinophilic cytoplasm, and were sometimes mini calcifications, with moderately atypical large nuclei, fine chromatin, and nucleolus. Mitoses were absent, without associated necrosis or vascular invasion.

The second component was formed by a proliferation of tangled bundles of varying density which were not vascular and nerve cells were made of corrugated cytoplasm and angular nucleus; the cell proliferation and scattered large cells, basophils, with large central nuclei, suggested vesicular ganglion cells with no signs of malignancy.

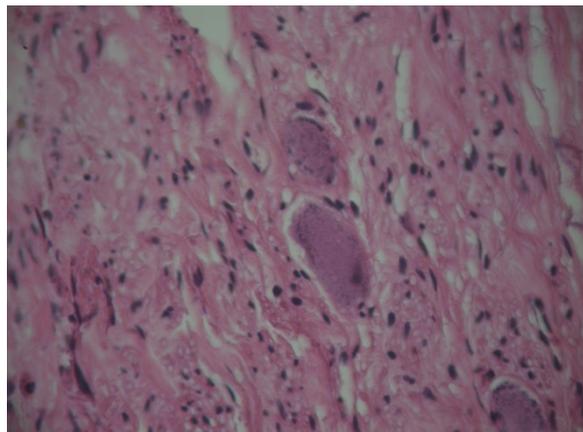


Figure 1. Microscopic findings of resected tumor

Tumor cells medium to large in size, with finely granular eosinophilic cytoplasm, and moderately atypical large nuclei, fine chromatin, and nucleolus.

The second fragment corresponds to an adrenal parenchyma. Immunohistochemical studies were performed: the pheochromocytes were positive to chromogranin, synaptophysin and PS 100 protein, while ganglion and neuronal cells were positive to antibodies of PS 100 and anti neurofilament.

3. Discussion

Composite tumors of the adrenal medulla are rare and typically consist of a predominant pattern of pheochromocytoma combined with ganglioneuroma, ganglioneuroblastoma, neuroblastoma, or, rarely, other components such as malignant peripheral nerve sheath tumor and neuroendocrine carcinoma [1,2,3]. The frequency of composite adrenal tumors has been reported as ranging from less than 3% of all adrenal gland neoplasms to between 1% and 9% of pheochromocytomas [4,5,6].

To date, less than 50 cases of composite pheochromocytoma have been reported [7,8,9]. Preoperative detection of a composite pheochromocytoma ganglioneuroma is difficult because of the low incidence of ganglioneuroma and because the symptoms are not different from those of typical pheochromocytomas [10]. In our case, our patient had hypertension and episodes of facial flushing, which led us to think that she had only pheochromocytoma. Little is known about the biological potential, outcome, or molecular genetics profile. The clinical symptoms associated with composite

pheochromocytoma-ganglioneuroma are usually similar to those of ordinary pheochromocytoma, but secretion of vasoactive intestinal polypeptides (VIP) is more common with composite pheochromocytoma-ganglioneuroma than with the former (ordinary pheochromocytoma) [11]. Hypertension and its related symptoms are common in composite pheochromocytoma ganglioneuroma. The fact that some patients may have composite tumors while being normotensive may be explained by the theory of autonomic regulation by ganglioneuroma, and it partially depends on the complex biochemical interaction and the proportion of each element [12]. Rarely, can watery diarrhea, hypokalemia and achlorhydria syndrome due to a functional VIP-secreting tumor be observed in patients with composite pheochromocytoma-ganglioneuroma; furthermore, the vasodilatory action of VIP contributes normotension [13]. In general, patients with pheochromocytoma are likely to develop papillary carcinoma, which may be related to the undulatory release of thyroid hormones as a result of circulating catecholamines [6,14]. Both pheochromocytoma and ganglioneuroma can commonly be radiologically seen as a well-defined, smooth or lobulated mass with or without calcification [10]. For our patient, a computed tomographic scan was performed, showing the presence of a spontaneously hypodense adrenal mass of 6 x 6 x 3 cm with microcalcification. Pathologically, the chromaffin cells of the pheochromocytoma are more readily highlighted with chromogranin A and synaptophysin staining and they are mixed with S-100 protein-positive sustentacular cells [15]. All the tumor cells of the pheochromocytoma portion of the composite tumor are strongly positive to tyrosine hydroxylase, i.e., the rate-limiting enzyme in catecholamine synthesis, while the ganglioneuroma portion displays neurofilament positive mature ganglion cells and S-100 protein-positive Schwann cells [10]. While pheochromocytoma is a tumor derived from chromaffin cells of the adrenal medullary, the ganglioneuroma is derived from the ganglionic cells or their precursors. For our patient, immunohistochemical studies were performed: the pheochromocytes were positive, to chromogranin, synaptophysin and PS 100 protein, while ganglion and neuronal cells were positive to antibodies of PS 100 and anti neurofilament. The histogenesis of composite adrenalmedullary tumors has been attributed to the common embryologic origin of chromaffine and neuronal cells from the neural crest and the inherent potential of chromaffin cells to undergo divergent cellular differentiation into neuronal elements [14]. Aberrant neural crest cell development has also been postulated as an etiologic factor, based on a number of cases that have occurred in a setting of neurocristopathies including neurofibromatosis type 1 [16,17] and multiple endocrine neoplasia type 2 [18].

A composite pheochromocytoma may develop as a result of loss of the neurofibromatosis type 1 gene product, neurofiromine, leading to abnormal Schwann cell proliferation with concomitant induction of chromaffin cell proliferation [19]. However, metastases have been reported in composite pheochromocytoma with ganglio-neuroblastoma and ganglioneuroblastoma [5,6]. Late recurrence of composite pheochromocytoma with ganglio-neuroblastoma has also been reported [20].

4. Conclusion

Composite pheochromocytoma is a rare variant of a relatively uncommon disease diagnosed by pathologists only. Fortunately, the treatment of such an entity remains the same as that for any pheochromocytoma.

Disclosure of Interest

The author declares that he has no conflicts of interest concerning this article.

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