

## Rare Case of Large Catecholamine Secreting Ganglioneuroma in an Asymptomatic Elderly Male

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### Abstract

Ganglioneuromas (GNs) are benign tumors that originate from neural crest cells, composed mainly of mature ganglion cells. These tumors, which are usually hormonally silent, tend to be discovered incidentally on imaging tests and occur along the paravertebral sympathetic chain, from the neck to the pelvis and occasionally in the adrenal medulla. Rarely, GNs secrete catecholamines.<sup>1</sup> Adrenal GNs occur most frequently in the fourth and fifth decades of life, whereas GNs of the retroperitoneum and posterior mediastinum are usually encountered in younger adults.<sup>2</sup> Adrenal GNs are commonly hormonally silent and asymptomatic; even when the lesion is of substantial size.<sup>3</sup>

We report an incidentally detected asymptomatic case of an adrenal ganglioneuroma with mildly elevated urinary catecholamine levels in an elderly male. After preoperative alpha blockade, the patient underwent open right adrenalectomy. Upon microscopic examination, the right adrenal mass proved to be a ganglioneuroma, maturing type and the immunohistochemistry examination showed immunoreactivity to synaptophysin, chromogranin, and CD 56, while S100 was strongly positive at the Schwannian stroma. Following resection, catecholamine levels normalized, confirming the resected right adrenal ganglioneuroma as the source of the catecholamine excess. This case represents a rare presentation of catecholamine-secreting adrenal ganglioneuroma in the elderly.

*Key words: adrenal glands, catecholamine, ganglioneuroma*

### INTRODUCTION

Ganglioneuromas (GNs) are benign tumors that originate from neural crest cells, composed mainly of mature ganglion cells. These tumors, which are usually hormonally silent, tend to be discovered incidentally on imaging tests and occur along the paravertebral sympathetic chain, from the neck to the pelvis, and occasionally in the adrenal medulla. Adrenal GNs occur most frequently in the fourth and fifth decades of life, whereas GNs of the retroperitoneum and posterior mediastinum are usually encountered in younger adults. GNs rarely secrete catecholamines, in contrast to pheochromocytomas and neuroblastomas. They also have different origins.

### CASE

A 72-year-old man was referred to our endocrine outpatient clinic for an incidentally detected right-sided adrenal mass following a computed tomography angiography of bilateral lower limbs done for workup of critical limb ischemia measuring 121 mm x 146 mm x 141 mm with an absolute washout of -150% and relative washout of -34%. There was no evidence of metastatic disease and no obvious invasion into adjacent structures. The patient

denied any paroxysmal symptoms and showed no clinical signs, except for hypertension for 20 years, well-controlled with a single agent. His urinary epinephrine (37.1 µg/day, normal range: 1.7-22.4 µg/day), norepinephrine (105.1 µg/day, normal range: 12.1-85.5 µg/day), and dopamine (587 mg/day, normal range: 64-400 mg/day) were all mildly elevated. Urinary HVA and VMA were not available. From the laboratory and imaging findings, the tumor was presumed to be a pheochromocytoma with suspected malignant potential.

The patient underwent preoperative alpha-adrenergic blockade with phenoxybenzamine two weeks prior to surgery followed by beta-blockade. The patient underwent open right adrenalectomy under general anesthesia. He had profound hemodynamic fluctuations during the operation and required vasopressor support for less than 24 hours postoperatively. He was discharged well on postoperative day 12.

On microscopic examination, the right adrenal mass proved to be a ganglioneuroma (maturing type) as there were areas containing mature ganglion cells which displayed eccentric nuclei, prominent single nucleoli with abundant eosinophilic cytoplasm with surrounding Schwannian

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**Table 1.** Differences in characteristics between pheochromocytoma, neuroblastoma, and ganglioneuroma

Characteristics	Pheochromocytoma	Neuroblastoma	Ganglioneuroma
Location	Adrenal	Adrenal, Paraspinal	Adrenal, Paravertebral sympathetic chain
Origin	Chromaffin cells	Neuroblasts	Neural crest cells
Urinary HVA, VMA, Metanephrines	Metanephrines more specific	Predominantly HVA and VMA <sup>4</sup>	Metanephrines, HVA, and VMA <sup>3,4</sup> (Rare)

HVA – Homovanillic acid; VMA – Vanillylmandelic acid

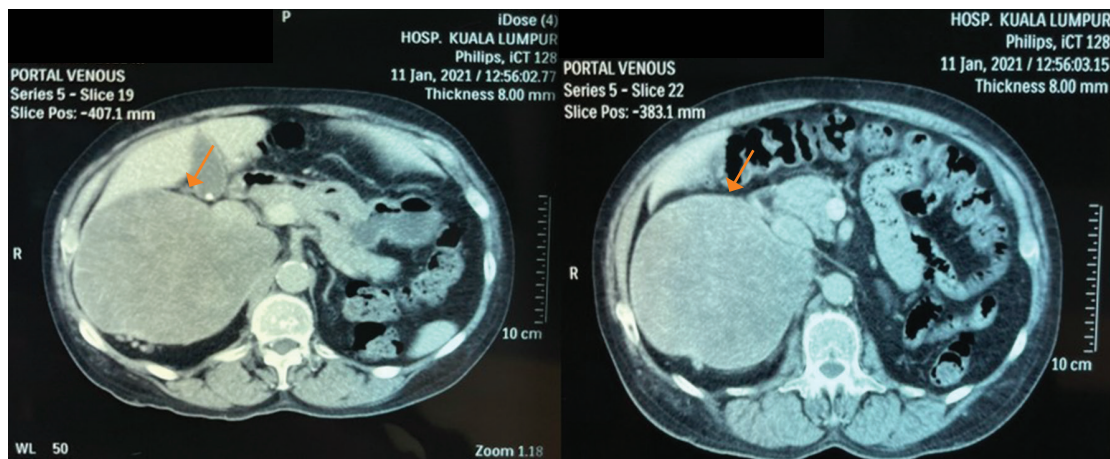
stroma and spindle cells. No mitosis was seen. Gold to brownish pigments were also seen in some neoplastic cells. No atypia, necrosis, or capsular breach was observed. No ganglioneuroblastic component or evidence of malignancy was seen. The immunohistochemistry examination showed immunoreactivity to synaptophysin, chromogranin, and CD 56 while S100 is strongly positive at the Schwannian stroma. They are negative for Pan Ck and GFAP.

## DISCUSSION

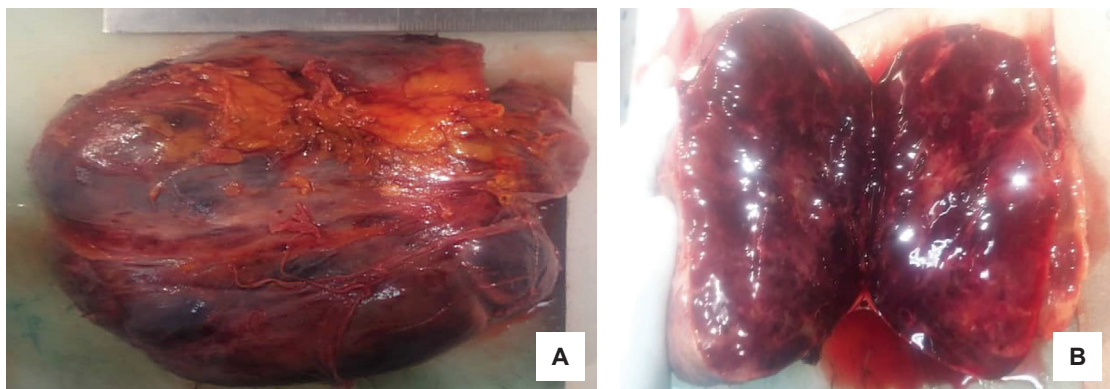
Ganglioneuromas are rare, benign, well-differentiated neural crest tumors arising in the paravertebral sympathetic chain, and are classically non-secretory and clinically asymptomatic.<sup>5</sup> Most ganglioneuromas are diagnosed incidentally on imaging. Patients may also present with

non-specific symptoms such as back or abdominal pain due to tumor mass effect. As with all incidental adrenal masses, a hormonal workup should be performed to determine the etiology of the tumor. Assessment should include evaluation of catecholamine or metanephrine levels, screening for cortisol excess, and measurement of plasma renin activity and aldosterone concentration.<sup>6</sup>

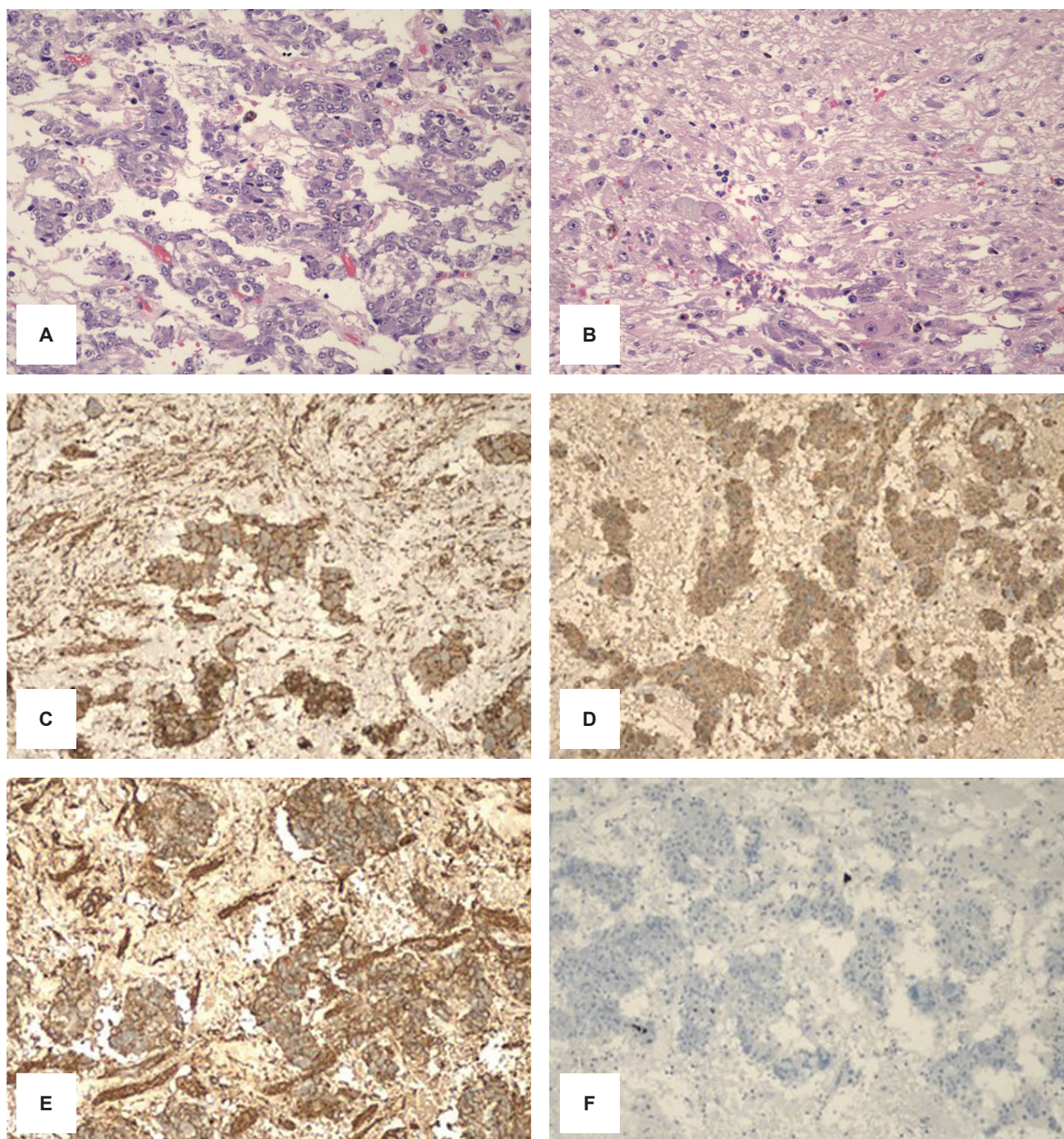
Ganglioneuromas are histologically benign lesions and can be classified into two main categories. The “mature type” GNs comprise of mature Schwann cells, ganglion cells, and perineural cells within a fibrous stroma whilst completely lacking neuroblasts and mitotic figures. The “maturing type” GNs consist of similar cellular populations with miscellaneous maturation degrees, ranging from fully mature cells to neuroblasts.<sup>7</sup>



**Figure 1.** Coronal Section Contrast-Enhanced CT Adrenal images in portovenous phase showing a large heterogeneous enhancing right adrenal mass with no calcification or fat component within (arrow). The density of the mass on the plain study is 41 HU, in portovenous phase 53 HU, and delayed study 71 HU.



**Figure 2.** Macroscopic findings. **(A)** Right adrenalectomy specimen: Large, well-circumscribed lobular mass weighing 1167 g and measuring 155 × 140 × 85 mm. The mass is smooth and shiny on the outer surface with some attached fatty tissues. Fine vessels are seen on its brownish-grey surface; **(B)** Right adrenalectomy specimen. Cut surface showing soft dark brownish multicystic areas with extensive hemorrhage. The cystic spaces range from 5-20 mm in diameter.



**Figure 3.** Histopathology of the mass. **(A)** Ganglioneuroma. The neoplastic cells are arranged in clusters set in loose fibrocollagenous stroma (H&E, 4x); **(B)** Ganglioneuroma. Neoplastic cells exhibiting mature ganglion cells with eccentric nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm with surrounding Schwannian stroma and spindle cells (H&E, 20x). Ganglioneuroma. Immunohistochemical stains show that the neoplastic cells are positive for **(C)** Synaptophysin, **(D)** Chromogranin, **(E)** CD56, and **(F)** negative for GFAP.

Although ganglioneuromas are thought to have no to low metabolic activity, several previous studies have reported high concentrations of catecholamines or MIBG uptake in intra- and extra-adrenal ganglioneuromas.<sup>8,9</sup>

It has been reported that up to 30% of patients with GNs may have elevated plasma and urinary catecholamine levels without exhibiting any symptoms of catecholamine excess.<sup>10</sup> Our patient was asymptomatic and definitely required surgical intervention for the large adrenal mass,

however, without adequate preoperative preparation, he would have been at risk for potentially fatal complications of the surgery. Thus, it is prudent to thoroughly investigate suspicious adrenal masses biochemically to avoid missing excess catecholamine secretion from the adrenal mass as significant morbidity and mortality can ensue intraoperatively if the patient is not adequately prepared for surgery. This patient made a remarkable recovery despite the stormy intraoperative and postoperative complications that ensued.

Composite pheochromocytoma–ganglioneuroma tumors are different, rare entities, consisting of both endocrine and neural components. Embryologically, both chromaffin and ganglion cells are derived from neural crest cells and migrate to somatic areas.<sup>11</sup> Immunohistochemically, the individual components of these tumors resemble their normal counterparts or pure tumors of the same type. Synaptophysin and chromogranin are strongly and diffusely positive in pheochromocytoma, while weak or focal in ganglioneuroma or neuroblasts. Staining for S-100 protein identifies spindle-shaped Schwannian cells and sustentacular cells while neurofilament only stains the neural part of the composite tumor.

Histologically, the endocrine component is that of a typical pheochromocytoma, whereas the neuronal component is characterized by mixed areas of ganglioneuroma, neuroblastoma, or ganglioneuroblastoma.<sup>12</sup> Our patient's histopathological examination did not reveal any chromaffin cells, excluding a pheochromocytoma–ganglioneuroma.

## CONCLUSION

This case illustrates that ganglioneuromas can grow to a significant size and present incidentally. They can be asymptomatic, as in our patient, who had a catecholamine secreting, histologically and immunohistochemistry confirmed maturing type of adrenal ganglioneuroma.

Following resection, catecholamine levels normalized, confirming the resected right adrenal ganglioneuroma as the source of the catecholamine excess. The patient made a remarkable recovery subsequently.

## Ethical Consideration

Patient consent was obtained before the submission of the manuscript.

## Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

## Author Disclosure

The authors declared no conflict of interest.

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None.

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