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CASE REPORT

# Unusual case of infrarenal pheochromocytoma developed on ectopic adrenal tissue: An autopsy case report

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**Introduction**: Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla. We describe an unusual case of pheochromocytoma located in the infrarenal area and associated with bilateral adrenal hyperplasia. **Case presentation**: A 70-year-old patient was admitted for syncope, diaphoresis, and high blood pressure. Computed tomography showed a 73x70x72 mm retroperitoneal mass of the left infrarenal area. High levels of metanephrine and noradrenaline were found in the urine. A tumor resection was performed. A few days after surgery, the blood pressure suddenly decreased and could not be restored, resulting in the death of the patient. Histopathological examination of the surgical specimen revealed a proliferation of monotonous cells, with eosinophilic cytoplasm, round nuclei with prominent nucleoli arranged in clusters, and capsular and vascular invasion. The tumor cells expressed synaptophysin and chromogranin, without positivity for inhibin A or S100 protein. At the autopsy, both adrenal glands showed hyperplasia but unrelated to the tumor mass. The histological aspect, location, and immunophenotype indicated an ectopic infrarenal pheochromocytoma. **Conclusions**: In patients with pheochromocytoma developed on ectopic adrenal tissue, clinical management might be difficult, and diagnosis can be sometimes established only based on post-mortem histopathological examination. Autopsy can be extremely useful in such cases with unexplained evolution.

**Keywords**: adrenal hyperplasia, pheochromocytoma, metanephrine

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## Introduction

Pheochromocytomas are catecholamine-secreting endocrine tumors originating from the chromaffin cells of the adrenal medulla. Pheochromocytomas that arise at extra-adrenal sites are called ectopic pheochromocytomas or paragangliomas, arising from chromaffin cells in sympathetic or parasympathetic ganglia. Pheochromocytomas used to also be known as 10% tumors because of the 10% rule: 10% have an ectopic origin, 10% are bilateral, 10% are in children, and 10% are malignant [1-3]. Most commonly, ectopic pheochromocytomas are located in the abdomen, followed by the thorax, pelvis, and neck. They originate in the ectopic adrenal tissue [1,2,4-7].

In this article, we describe a rare case of ectopic pheochromocytoma located in the retroperitoneal, infrarenal area and associated with bilateral adrenal hyperplasia.

## Case report

A 70-year-old male cardiac patient presented complaining of repeated syncope in the four days before presentation, palpitations, abdominal pain, diaphoresis, and paroxysmic hypertensive crisis.

Computed tomography (CT) indicated a para-aortic tumor 7.3 cm in diameter, located below the left kidney. The tumor mass had a polylobate aspect, with solid and cystic areas. For biochemical diagnosis, urinary free metanephrine and catecholamine levels were measured (Table 1).

Considering the patient's clinical symptoms as well as the laboratory findings and imagistic report, surgical treatment was decided for the tumor, which as suspected as a retroperitoneal sarcoma of the left intrarenal area, penetrating the psoas. The tumor was sent to the pathology department for histopathological evaluation.

The fragmented tumor specimens showed a red-brownish hemorrhagic cut surface. They proved microscopically to consist of a proliferation of small cells, with monotonous aspect, eosinophilic cytoplasm, round nuclei, and prominent nucleoli. Areas of large tumor cells with abundant eosinophilic cytoplasm and pleomorphic nuclei represented below 20% of the tumor cells (Fig. 1). Large areas of hemorrhage were observed, along with vascular invasion and infiltration of the capsule. On the periphery of the tumor, a small area represented by the cortex of the adrenal gland was observed, without remnant medulla.

The tumor cells displayed positivity for synaptophysin and chromogranin A. They did not express inhibin or S100 protein (Fig. 1). The Ki67 proliferation index was below 2% in the tumor cells. The histological aspect and immunophenotype indicated an infrarenal pheochromocytoma that was probably developed on ectopic adrenal tissue.

During the first days after the surgery, the patient was stable, but death happened at eight days postoperatively.

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Table 1. Urinary-free metanephrine and catecholamine values

| Parameter | Normal Ranges (mcg/24h) | Patient's Values (mcg/24h) |
|---|---|---|
| Noradrenaline | 15-80 | 834880 |
| Metanephrine | 24-96 | 726180 |
| Normetanephrine | 75-375 | 15476240 |

At the autopsy, we identified bilateral adrenal hyperplasia, without remnant tumor cells, pulmonary dystelectasis with bilateral disseminated bronchopneumonia, fibrinous pleuritis, and fibrino-purulent peritonitis. Systemic atherosclerosis and concentric ventricular hypertrophy were associated, the latter being an indicator of systemic hypertension.

Because the adrenal gland hyperplasia was not related with the infrarenal mass, which was completely excised, and peritumoral adrenal cortex was identified, the case was interpreted as a pheochromocytoma developed on ectopic infrarenal adrenal gland. Signed informed consent was obtained from the relatives to perform the autopsy and publish the scientific data.

## Discussion

Because of the high production of catecholamines, patients with pheochromocytoma can present with hypertension associated with episodic headache, sweating, and tachycardia, referred to as the classic triad [5,6,8]. Not all cases present with such manifestations [5].

Extra-adrenal pheochromocytoma should be differentiated from a paraganglioma and from an endocrine tumor developed from ectopic adrenal gland. If primary pheochromocytoma arises from the chromaffin cells of the adrenal medulla, paraganglioma is an extra-adrenal pheochromocytoma derived from extra-adrenal chromaffin cells of sympathetic or parasympathetic paraganglia. Paraganglioma is most found in the abdomen, thorax, and pelvis and less frequently in the head and neck area [1,2,9,10].

In the case of aberrant adrenal gland organogenesis, ectopic adrenal tissue can be found, and it usually exclusively contains the adrenal cortex [11]. This occurs when during development, a fragment of the primitive adrenal gland separates. Both cortex and medulla can be present in the ectopic adrenal tissue, if the separation takes place in a later phase during organogenesis, after the neural crest's migra-

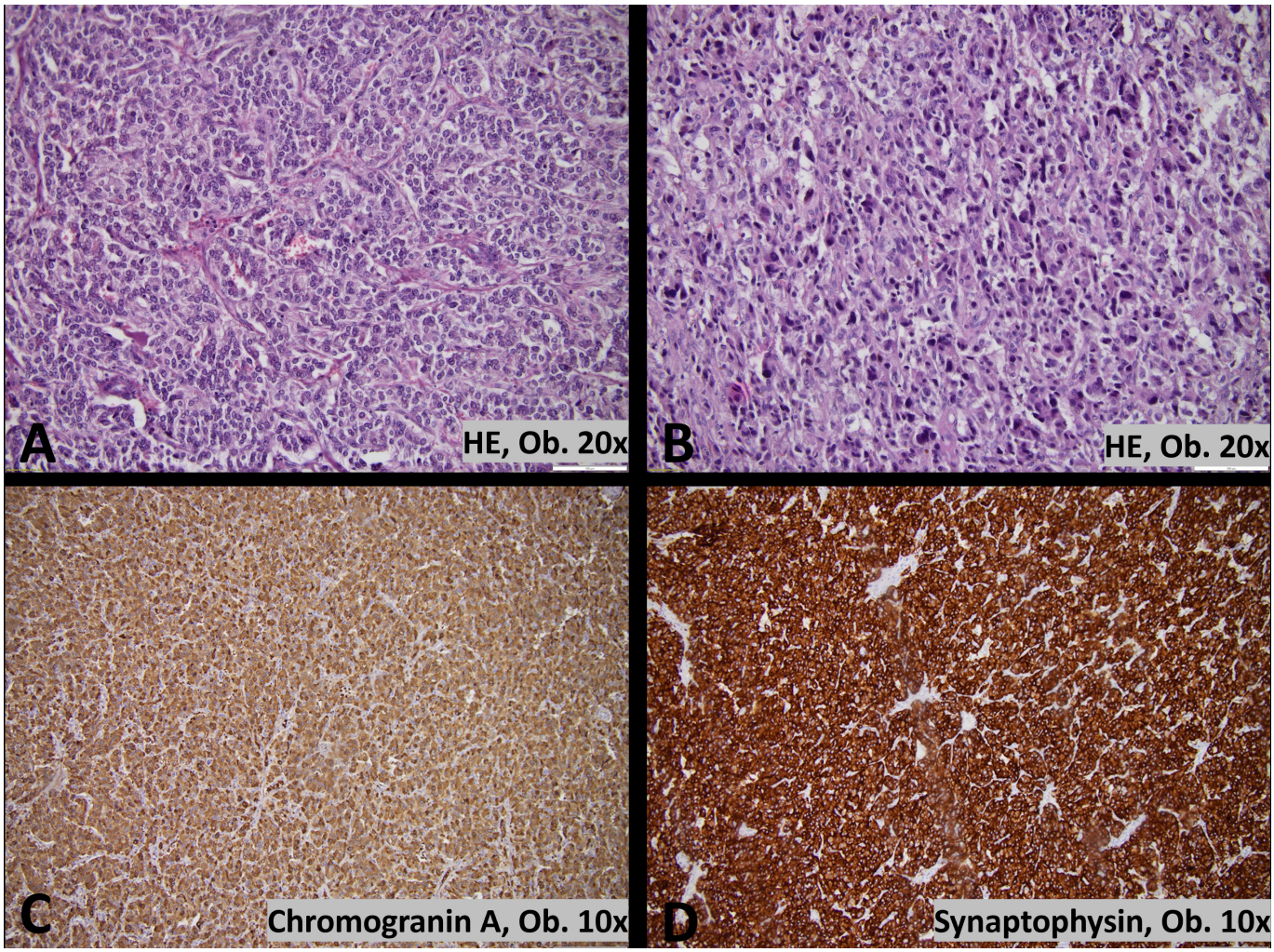


Fig. 1. Microscopic view of pheochromocytoma. The tumor consists of small tumor cells, with monotonous aspect, eosinophilic cytoplasm, and round nuclei with prominent nucleoli (A), alternating with areas of large cells, with pleomorphic nuclei (B). The tumor cells express chromogranin A (C) and synaptophysin (D).

tion into the cortex. Usually, the medulla might be found in the ectopic tissue when the separation takes place near the location of the normal adrenal glands [7,12-15].

Pheochromocytoma can be sporadic or hereditary. Several genetic syndromes are known to be associated with a high risk of pheochromocytoma. Some of these syndromes are multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease, and neurofibromatosis type 1 [4].

MEN2 syndrome is an autosomal inherited disorder associated with mutations of the RET protooncogene. Around 50% of patients with MEN2 are known to develop pheochromocytoma, and the tumor occurs bilaterally in approximately 50-60% [6,12]. Additionally, cases of adrenal medullary hyperplasia, a benign non-catecholamine-secreting lesion, have been described in patients with MEN2 syndrome. Adrenal medullary hyperplasia is usually described in hereditary pheochromocytoma syndromes due to surveillance. Korpershoek et al. showed that MEN2-associated pheochromocytoma exhibits genomic alterations identical to adrenal medullary hyperplasia in MEN2 syndrome, suggesting that adrenal medullary hyperplasia could represent a precursor lesion for pheochromocytoma [13]. Recently, Ohsugi et al. described a case of bilateral adrenal pheochromocytoma associated with ectopic adrenal medullary hyperplasia that 12 months later developed into a pheochromocytoma, in a patient with MEN2A syndrome [14]. All patients with a diagnosis of pheochromocytoma should be considered for genetic screening [6,16]. In our case, the patient was diagnosed with a retroperitoneal pheochromocytoma developed on ectopic adrenal tissue associated with bilateral adrenal medullary hyperplasia.

Pheochromocytoma is generally a malignant tumor, with only 10% being metastatic. Besides the risk of metastasis, pheochromocytoma represents a life-threatening condition due to catecholamine overproduction. Acute cardiac complications related to pheochromocytomas and paragangliomas encompass arrhythmias (bradycardia and tachycardia), Takotsubo-like cardiomyopathy, dilated cardiomyopathy, thromboembolism, and acute coronary syndrome. Symptoms of catecholamine excess may include palpitations, headache, sweating, and pallor, usually associated with hypertension [1]. Plasma-free metanephrines provide the best investigation and should represent the first course of action in diagnosing the tumor [17,18]. Another reliable biochemical test involves measurements of 24-h urinary excretion of free catecholamines or catecholamine metabolites. In the absence of catecholamine production and therefore of any clinical symptom, the tumor is often incidentally detected on a CT scan [17,19]. Despite the high accuracy of biochemical analysis and imaging investigations, histopathological examination remains the gold standard for the final diagnosis.

Due to the nonspecific symptoms or the ectopic location, the diagnosis is frequently inaccurate or delayed. The standard curative procedure for pheochromocytoma is prompt surgical resection. Large amounts of catecholamines could be released during anesthesia induction, intubation, and manipulation of the tumor [20]. Therefore, appropriate preoperative preparation is crucial because resecting a catecholamine-secreting tumor represents such a high-risk procedure. For preventing any perioperative cardiovascular complications, the first-choice recommendation is to use α-adrenergic receptor blockers at least eight days preoperatively. To prevent severe and sustained hypotension after the removal of the tumor, the preoperative treatment should include a high-sodium diet and fluid intake [18].

## Conclusions

Ectopic pheochromocytoma is a catecholamine-producing tumor whose removal may be associated with significant morbidity and mortality. Because nonspecific symptoms can be associated, some cases are discovered at autopsy. The particularity, in this case, was related on the location of the tumor alongside the bilateral adrenal hyperplasia, and its pre-operatory evaluation as a retroperitoneal sarcoma.

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## Authors' contribution

RC: conceptualization, writing – original draft, formal analysis, performing autopsy

IJ: investigation, validation of histological and immunohistochemical stains

TB: surgical intervention, data curation, literature review

SG: histopathological diagnosis, writing – review and editing, project administration, supervision

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