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A Rare Case of a Retroperitoneal Paraganglioma: A Case Report

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Abstract **Case Report**

Retroperitoneal paraganglioma is a rare neoplasm that develops from chromaffin cells that secrete catecholamines in the sympathetic ganglia. They are frequently functional and may be benign or malignant depending on the presence of metastasis and/or the occurrence of recurrence. Different imaging modalities play a crucial role in detecting these tumors. The typical CT appearance of PG is that of a well limited isodense mass with an intense contrast enhancement. On MRI, the mass presents an isosignal or hyposignal in T1 and hypersignal in T2 with an early and intense enhancement. The final diagnosis is based on histological and immunohistochemical findings and the surgical excision is the mainstay of the treatment. However, these tumors are often difficult to diagnose and treat. We report a case of a 30-year-old female patient who presented with a 3 months history of constipation, revealing on computed tomography (CT) a retroperitoneal mass lateralized on the right with a close connection to the inferior vena cava. Urine normetadrenaline (metanephrine) was elevated at 451 ug/24h. Neck and chest CT scan and scintigraphy with 123-I labeled metaiodobenzylguanidine (MIBG) were negative. Complete resection of the tumor was performed. The histological examination and immunohistochemical analyses concluded the diagnosis of a paraganglioma.

Keywords: Retroperitoneal paraganglioma, neuroendocrine tumor, CT, MRI, laparotomy, surgery.

INTRODUCTION

Paragangliomas (PGs) are rare neuroendocrine tumors which are derived from paraganglia, a diffuse neuroendocrine system resulting from the migration of specialized neural crest cells [1]. These neoplasms can be found within the skull base, neck, chest, abdomen and pelvis. They are mostly seen in thoracic and abdominal sympathetic nerves. More specifically, the retroperitoneal paraganglioma accounts for over 50% of all paragangliomas [2]. They arise from the sympathic chain and are usually found within para-aortic and peri-nephric spaces [3].

Retroperitoneal PG can occur at any age, most commonly in young adults and tend to be sporadic [4].

However, they can be linked to syndromes in approximately 30% [5]. They may be functional and result in symptoms of excess catecholamine production. Approximately 10-15% of such tumors is non-functional, and in another 10% hormone activity is not manifest clinically. They are frequently locally invasive and have a high incidence of local recurrence [6].

The radiological diagnosis is based on computed tomography (CT) and magnetic resonance imaging, (MRI). Since benign and malignant retroperitoneal PG have both the same histological appearance, the best predictor of malignancy is metastasis or recurrence [7]. The possibility of malignant transformation of paragangliomas makes surgical excision the treatment of choice. The adjuvant radiotherapy and chemotherapy are often used in metastatic PG but without significantly influencing the prognosis.

We present a case of a 30-year-old patient with a functional retroperitoneal paraganglioma discovered during investigation of constipation.

CASE PRESENTATION

A 30-year-old woman presented with a 3 months history of constipation. The patient had no

significant history of hypertension and denied clinical symptoms such as headaches, palpitations or sweating attacks. The patient had no particular family history.

Clinical examination was unremarkable with no palpable abdominal mass present. Routine laboratory tests results did not demonstrate any abnormalities. Abdominal ultrasonography showed a rounded mass in the projection of the pancreatoduodenal junction, heterogenous with a solid and fluid component and vascularized with color doppler ultrasound. An esophagogastroduodenoscopy was performed and didn't reveal a duodenal mass.

To better characterize this mass, CT of the abdomen and pelvis after the injection of an intravenous contrast agent (PDC) was performed and revealed a well-defined retroperitoneal mass lateralized on the right, round shaped, with regular contours, spontaneously hypodense and heterogeneous (Figure 1), intensely and heterogeneously enhanced after injection of PDC in the arterial phase (Figure 2), delimiting liquid areas, with progressively washing in the portal and late phases. The mass measured 30 x 29 x 37 mm and had close connection to the inferior vena cava (IVC) and the right renal vascular pedicle (Figure 3 and 4). It was also intimately related to the head of pancreas and the right kidney but not infiltrating them. There was no lymphadenopathy. These findings were more consistent with a retroperitoneal neuroendocrine tumor.

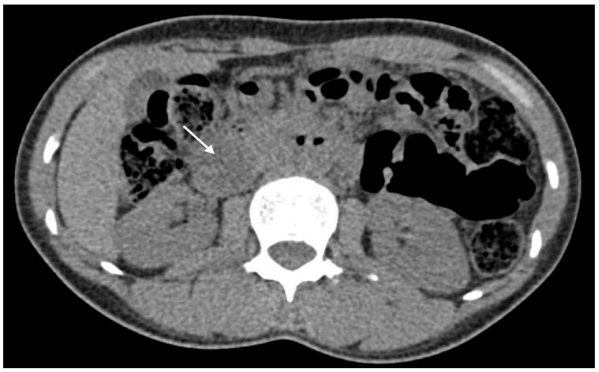

Figure 1: Abdominal CT scan without PDC injection, axial sequence: well-defined retroperitoneal mass (white arrow), lateralized on the right, round shaped, with regular contours, spontaneously hypodense and heterogeneous.

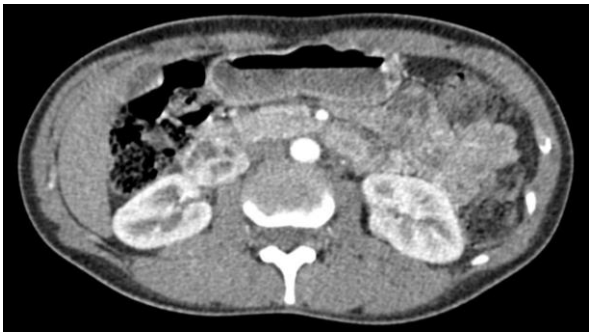

Figure 2: Abdominal CT scan with PDC injection: arterial phase, axial sequence: the mass is intensely and heterogeneously enhanced after injection of PDC (the solid component).

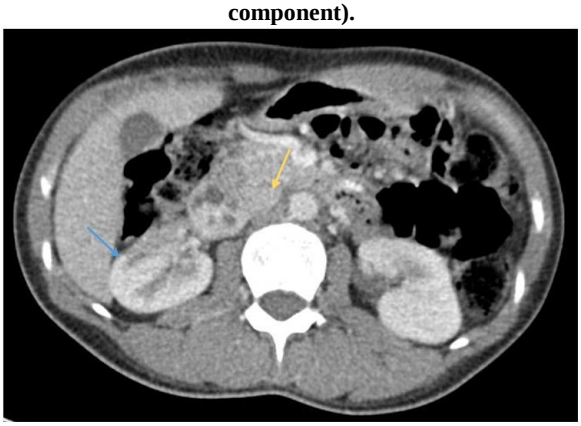

Figure 3: Abdominal CT scan with PDC injection: portal phase, axial sequence: the mass is adjacent to the right kidney (blue arrow) and the IVC (yellow arrow), with discrete washing.

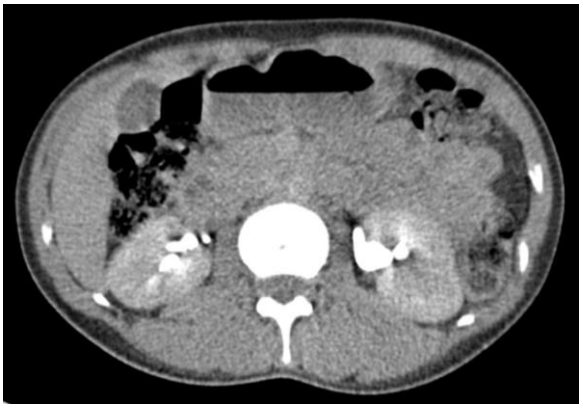

Figure 4: Abdominal CT scan with PDC injection: late phase, axial sequence: late washing of the mass.

Neck and chest CT scans were unremarkable. Urine normetadrenaline (metanephrine) was elevated at 451 ug/24h (normal range < 51 ug/24h). Scintigraphy with 123-I labeled metaiodobenzylguanidine (MIBG) was also negative.

The lesion was completely resected through a right subcostal laparotomy incision. The mass was located inferior to the right renal vein, medial to the right kidney and lateral to the IVC. The mass did not seem invading into any surrounding structure (Figure 5). Postoperative course was uneventful.

On macroscopic examination, the mass was encapsulated with a firm consistency measuring 3 x 1,5 x 2,5 cm (Figure 6). The histopathology study raised a suspicion of paraganglioma. The immunohistochemical staining studies were positive for neuroendocrine markers: PS100, chromogranin and synaptophysin (Figure 7 and 8). As a result, a final pathologic diagnosis of paraganglioma was issued with a GAPP score (Grading of Adrenal Pheochromocytoma and

Paraganglioma) estimated to 2 (well differentiated type) which is in favor of a low risk of metastasis.

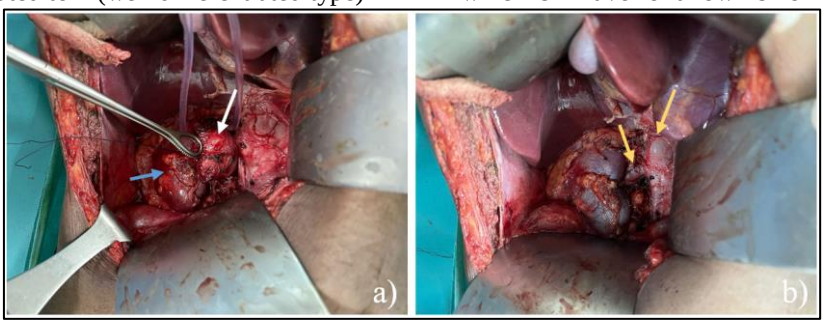

Figure 5: Intraoperative image of the paraganglioma (before (a) and after the resection (b)): the mass (white arrow) was adjacent to the right kidney (blue arrow) with intimate contact to the IVC and the right renal vein (yellow arrows)

Figure 6: Macroscopic view of the specimen: showing the diameter of the resected tumor

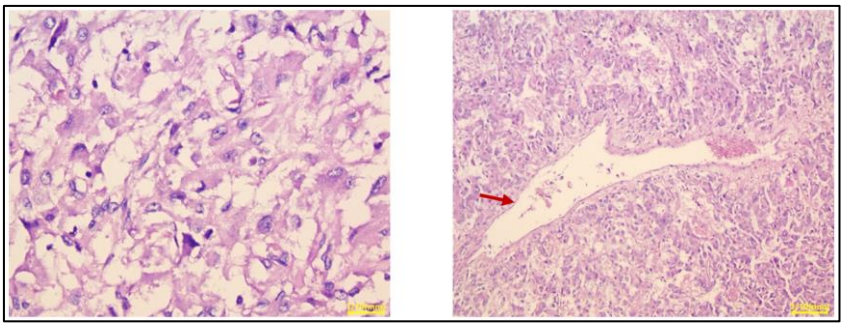

Figure 7: Histopathological study of the tumor (microscopic study): showing nets of round, oval to polygonal tumoral cells with central nuclei and eosinophilic cytoplasm, separated by highly vascularized fibrous septa (red arrow)

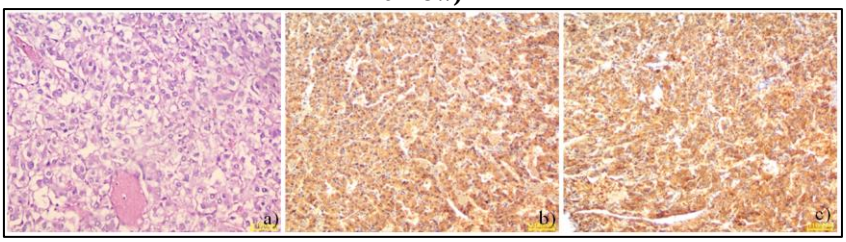

Figure 8: Histopathological study of the tumor (immunohistochemical study): cells expressing PS100 (a), chromogranin (b) and synaptophysin (c)

DISCUSSION

Paragangliomas or extra-adrenal pheochromocytomas are a subset of rare neuroendocrine tumors that originate from the extra-adrenal chromaffin cells. They are grouped based off their origin in the parasympathetic or the sympathetic nerve tissues within paraganglia [1, 2]. Parasympathetic paragangliomas typically arise from tissue in the head and neck, including the carotid body, vagus nerve, and jugular foramen. Sympathetic paragangliomas are most common in the abdomen, pelvis, and chest. About 70% of sympathetic paragangliomas are intraabdominal,

usually found in the perinephric and paraaortic spaces (organ of the Zuckerkandl) [3].

The exact incidence of retroperitoneal paragangliomas is unknown. The median age of diagnosis for retroperitoneal paragangliomas is 37- 43 years and the distribution between male and female patients is balanced (1:1) [8]. A large proportion of paragangliomas (40 %) are related to hereditary syndromes, such as Von Hippel-Lindau (VHL) gene mutations, multiple endocrine neoplasia type 2 (MEN2) … [5]. These hereditary forms tend to have a male predilection, to be multifocal and with increased risk of recurrence and metastasis.

Clinical manifestations of paragangliomas vary depending on the tumor's location and size, catecholamine secretory function, and extent of spread. Functional retroperitoneal PG synthesize, store, and secrete catecholamines. This results in elevated levels of urine/serum catecholamines and typical triad of clinical symptoms: episodic headaches, profuse sweating, and palpitations [9]. Non-functional retroperitoneal PG are distinguished by their asymptomatic profile and normal catecholamine levels in the urine and blood [10]. A large proportion of these tumors are incidentally discovered in normotensive patients during imaging evaluation for other reasons or may be discovered in the presence of atypical compressive symptoms such as abdominal pain that may be associated with nausea, vomiting, abdominal distension, constipation, urinary symptoms and weight loss [11]. Thus, the diagnosis of non-functional PG is often, delayed. Our patient did not have the specific symptoms of catecholamine hypersecretion.

PGs are usually benign. However, they can be locally invasive. They can also turn malignant with distant metastasis. Paragangliomas metastasize approximately in 20% to 42% of the cases. The most common site of metastasis is the regional lymph nodes, bone, lung, liver and spleen [12]. The presence of metastases or the occurrence of recurrence is the only reliable criterion to distinguish benign from malign PG [7].

In patients who present with symptoms suggestive of excess catecholamine production, laboratory tests can help detect active tumor secretion of epinephrine and norepinephrine by measuring catecholamines and related metabolites in the plasma and urine [13].

Radiologically, imaging plays a crucial role in the diagnosis, local-regional extension assessment, preoperative planning and monitoring of retroperitoneal PG. Doppler color ultrasound may be used as a first-line investigation and demonstrates the highly vascular nature of these tumors, however CT and MRI have higher sensitivity [14]. The imaging modality of choice for primary tumor evaluation and staging is a CT of the thorax, abdomen, and pelvis. If no lesion is found, further imaging of the organ of Zuckerland and the bladder is performed.

The CT of the abdominal and pelvis reveals a well-limited soft-tissue mass along the retroperitoneal path of the sympathetic nervous system, with a median size of 3 to 5 cm in the early stages of the disease. The spontaneous density is greater than 10 Hounsfield Units (HU) (isodense to the muscle) and the lesion enhances strongly and precociously on arterial time, sometimes heterogeneously. Smaller tumors are more likely to be homogeneous in attenuation and sharply marginated as compared with larger ones. Areas of intralesional hemorrhage, necrosis and calcifications can be frequently seen as the tumor enlarges [15]. Angiography may be useful in revealing vascular invasion or in demonstrating small metastases [16].

MRI is more sensitive than CT in detecting extra-adrenal tumors [17]. It is typically reserved for those with likely metastatic PG or those with contraindications for using intravenous contrast agents during computed tomography. The protocol should include diffusion, T2, T1 and T1 after injection of Gadolinium sequences. Additional in-phase and out-of-phase sequences may help in the differential diagnosis with certain other adrenal lesions. PGs are usually hypointense or isointense compared with the liver parenchyma on T1-weighted MRI with an early and intense enhancement after injection of Gadolinium. On T2-weighted sequences, they exhibit high signal intensity and are sometimes heterogeneous including necrotic areas. No drop in signal is observed on the out-of-phase sequence [18].

Scintigraphy with 123-I labeled MIBG offers superior specificity than CT and MRI imaging. It is used for the detection of multiple primary tumors, tumors outside the usual locations, or metastases [19].

The definitive diagnosis of PG can only be confirmed with histological and immunohistochemical evaluation [20]. Histologically paragangliomas are diagnosed by their highly vascular appearance, with chief cells and sustenacular cells arranged in clusters called zell-ballen. It is this rich vascular component of the tumor that explains the intense contrast enhancement at CT or MRI imaging. Specific antibodies for neuroendocrine markers such as synaptophysin and chromogranin, as well as S-100 protein, may also be used to confirm the diagnosis [8].

Clinical risk factors of metastasis and/or multiple tumors include young age at diagnosis (<40 years), extra adrenal location, tumor size greater than 5 cm, presence of a mutation in one of the SDH genes and preferential elevation of normetanephrine [21]. Pathologic risk factors used to predict metastasis and

survival have been included in scoring systems such as the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP), with a score ranging from 0-2 (well differentiated type), 3-6 (moderately differentiated type), to 7-10 (poorly differentiated type). The higher the GAPP score, the greater the risk of metastasis. In all these situations, functional whole-body imaging is recommended [22].

Because of the risk of malignant transformation of paragangliomas, and since these tumors do not respond well to chemotherapy or radiation therapy, surgical excision is the mainstay of treatment with radical resection possible in 75% of cases [19]. The tumor's resection can be preceded either by laparoscopy (for small non-invasive tumor) or laparotomy (for large tumor) after adequate preoperative medical preparation. Aggressive surgery is mandatory to obtain disease free survival.

Some paragangliomas represent a challenge in management. High vascularity, huge size and critical location near vital blood vessels can cause surgical resection to carry a very high risk of complications or even death. If a tumor is surgically unresectable, it is recommended to reduce its size by using chemotherapy, radiation therapy, or embolization [23].

For patients with metastatic paraganglioma, resection is not a therapeutic option even if it offers the only chance of cure. In this case, the therapeutic options are chemotherapy, MIBG therapy, external irradiation for bone metastases, and targeted molecular therapy like tyrosine kinase inhibitor [12]. Other options in treating inoperable paragangliomas are octreotide and radionuclide therapy with radioactive iodine coupled with MIBG. These complementary therapies can ensure a positive response in 50% of the cases but without any significant influence on prognosis (24).

Surgery is the only mean that allows a significant improvement in prognosis with a five-year and ten year survival rate without relapse of 75% and 45% respectively. In the case of metastatic forms, the median survival duration is three years and in the case of incomplete resection, the median overall survival is approximately four years [25].

Postoperative monitoring with CT/MRI and PET scans is recommended in order to detect malignant potential or progression of the disease. This should begin three months after surgery and continue biannually for the first three years. The total duration of follow- up recommended is at least ten years for PGs and if there is a high risk of malignant PG, the follow-up must be extended. A life follow-up is even advised in this case [26].

CONCLUSION

Retroperitoneal paragangliomas are rare neuroendocrine tumors, mostly benign with good prognosis. Recurrence and metastasis define the malignant forms. Functional tumors may present with typical symptoms such as palpitations, headaches and profuse sweating.

Patients should be initially evaluated with catecholamine levels, followed by CT or MRI to locate the primary lesion. The characteristic appearance of retroperitoneal PG on imaging is that of a well limited mass with an early and intense enhancement. The final diagnosis is based on histological and immunohistochemical findings.

While surgical resection remains the treatment of choice for the localized tumors, there are some therapeutic options for those with metastatic disease.

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