

World News of Natural Sciences

An International Scientific Journal

WNOFNS 21 (2018) 9-15

EISSN 2543-5426

Voluminous Pheochromocytoma suspected of malignancy: a difficult diagnosis and an uncertain prognosis. About a case

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ABSTRACT

Pheochromocytomas are rare tumors arising from the adrenal medulla. The diagnosis of malignancy remains a dogma between surgeon, pathologist and oncologist. We present a case of voluminous pheochromocytoma in a 53-year-old female patient, suspect of malignancy in the pathologic examination, while emphasizing the importance of the clinical and radiological long-term monitoring.

Keywords: pheochromocytoma, malignancy, diagnosis, treatment

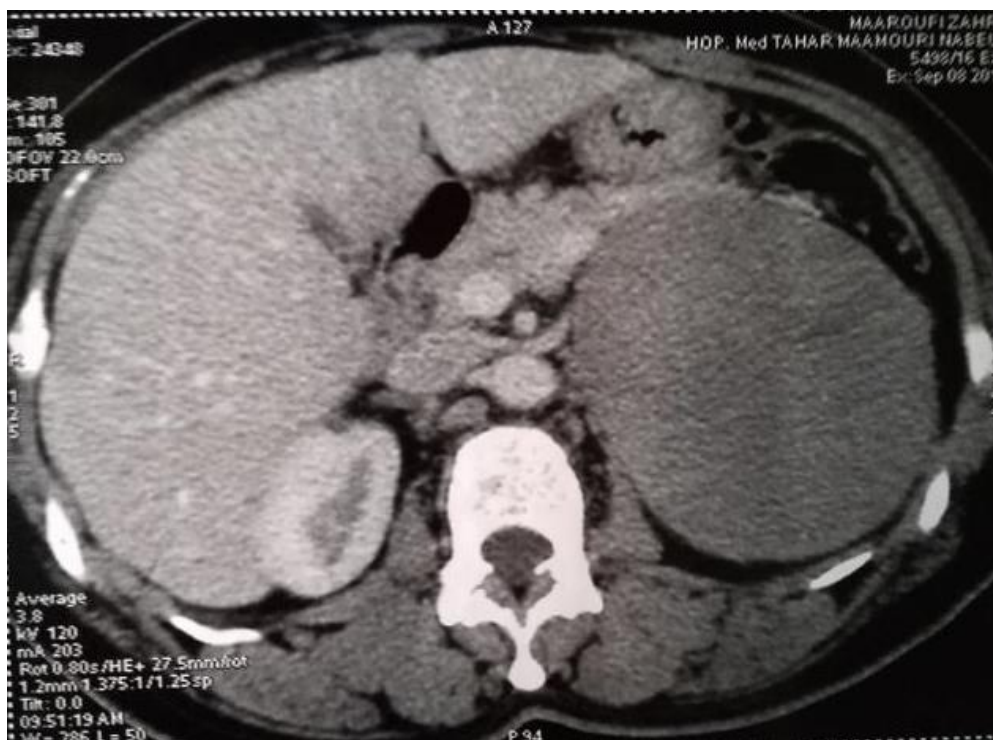
1. INTRODUCTION

Pheochromocytomas are rare tumors, arising commonly from the chromaffin cells of the adrenal medulla. These cells synthesize and store catecholamines which high levels are responsible for the clinical manifestations. A paraganglioma is a tumor that is developed from the extra-adrenal chromaffin tissue, that may or may not secrete catecholamines. Only the presence of distant metastases in a site free from chromaffin tissue, the tumor infiltration or the locoregional recurrence may confirm the diagnosis of malignancy.

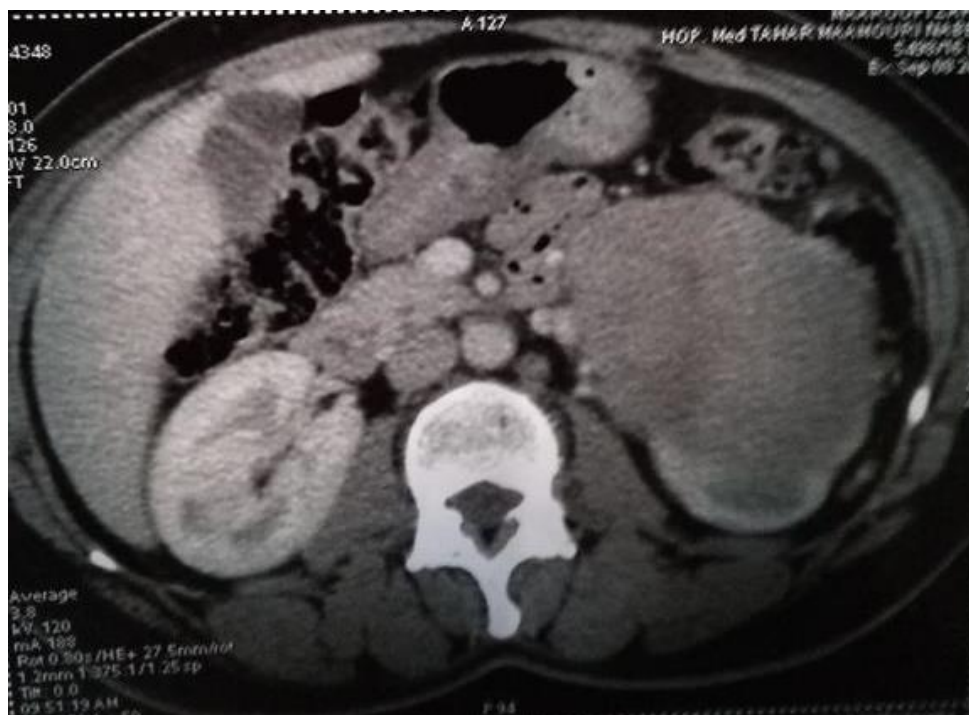
Within a case report and a literature review, we will be discussing the difficulties encountered in the diagnosis of malignant pheochromocytomas and their various therapeutic approaches while emphasizing the importance of long-term monitoring.

2. OBSERVATION

A 53 year-old female patient, with a medical history of acute coronary syndrome, presented with headaches, palpitations and left lower back-pain for the past year. Physical examination showed no particular findings apart from paroxysmal hypertensive peaks (Maximum BP : 180/100 mmhg). A CT-scan demonstrated a 14×10 cm heterogeneous well-limited adrenal mass with a pre-contrast attenuation of 35HU and an absolute contrast wash-out of 4.5% with no sign of loco regional aggressiveness (Figure 1). Laboratory tests showed elevated serum levels of metanephrines and normetanephrines (respectively 16 and 27 times higher than the normal range). A left costal incision allowed the removal of a 15cm, well-limited and encapsulated adrenal tumour ((Figure 2). Intraoperatively, several hypertensive peaks (around 210/110 mmhg) were noted during surgical handling of the tumour. The postoperative period was uneventful. The histopathological and immunohistochemical examination of the resected piece concluded to a giant pheochromocytoma with an elevated aggressiveness score (Pheochromocytoma of the Adrenal gland Scaled Score PASS=5) and a capsular invasion (Figure 3). A Metaiodobenzylguanidine (MIBG) scintigraphy performed 3 months later did not identify any extra-adrenal localizations of the pheochromocytoma.



(A)



(B)

Figure 1(A,B). Abdominal CT-scan: adrenal mass of over 14 cm without signs of loco regional aggressiveness.



Figure 2. Resected piece: Encapsulated oval adrenal tumour of 15 cm.

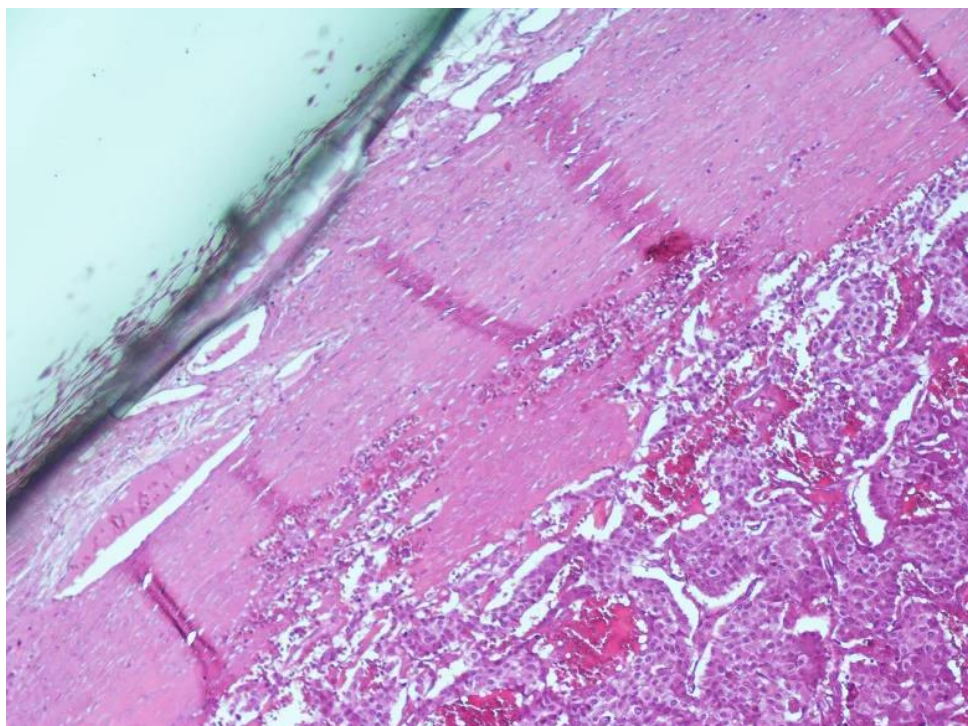


Figure 3. High magnification: Partial infiltration of the capsule without exceeding it.

3. DISCUSSION

Malignant pheochromocytomas (MPC) represent for about 10% of all pheochromocytomas [1]. Malignancy is relatively more common for paragangliomas (30-40%) [2]. Clinically, there is no difference between benign and malignant pheochromocytomas. Regarding the biological diagnosis, several abnormalities, such as the dopaminosecretion and the intra-tumoral concentration of EM66 (chromogranin C), were studied to establish the diagnosis of malignancy, however, the findings were conflicting. [3, 4].

The CT-scan remains the test of choice for locating a Pheochromocytoma. An absolute and relative washout, below respectively 60% and 40%, and the presence of adenopathies must suspect malignancy [5]. For our patient, the important size of the tumour as well as the much delayed (4.5%) absolute wash-out can orient towards the malignant nature of the mass [6]. The MRI is as efficient as the CT-scan [5, 7]. MIBG scintigraphy seems more reliable in the detection of paragangliomas and metastases with a specificity of 92% and a sensitivity of 100% [8]. According to Ilias and al [9], PET-Scan appears to be better than scintigraphy in the diagnosis of malignancy.

Histologically, MPCs are macroscopically characterized by tumour necrosis and capsular and vascular invasion, and microscopically by their endocrinoid and fusiform appearance, with the presence of mature lymph node cells [10]. While synaptophysin, vimentin, and S-100 protein labelling characterizes all pheochromocytomas, chromogranin and Ki 67 labelling is currently more distinctive for malignant forms, but the sensitivity is

only 50% [10, 11]. For our patient, immunohistochemical labelling using chromogranin was positive with a low Mib1 / Ki67 proliferation index (2%).

Some authors have proposed aggressiveness scores, such as that of Thomson's 'PASS', which has been validated by several studies [11, 12]. Tumour size, PASS score and capsular invasion (Figure 3) point to the aggressive nature of the tumour in our patient without confirming its malignancy. The majority of MPC is sporadic (75%) [2], yet they can be associated with genetic familial syndromes: Von-Hippel-Landau disease, multiple endocrine neoplasia type 2, neurofibromatosis type 1, Sturge-Weber syndrome, tuberous sclerosis [2].

Treatment of metastatic MPC remains difficult and sometimes disappointing. Surgery represents the main element [2, 13]. Its objective is to perform an adrenalectomy associated with metastasectomies. The aim is to decrease the production of catecholamines and reduce the tumour volume for a possible adjuvant treatment [2, 13].

The trans or retroperitoneal laparoscopic approach is limited to small tumours without local invasion [2]. Lateral aortic lymph node dissection on the left, latero cave on the right and a dissection of the renal pedicle are systematically associated. In case of positive scintigraphy, ¹³¹I-MIBG metabolic radiotherapy is indicated as an adjuvant therapy with variable tumour responses (24 to 45%) and a low toxicity rate [2]. Chemotherapy is indicated either for non-operable tumours or in case of failure of the metabolic radiotherapy.

The most widely used chemotherapy protocol is a cyclophosphamide-vincristine-dacarbazine combination with a biological response rate of 0 to 78% and a partial tumour response of 0 to 50% [2]. Careful sustained clinical, biological and morphological follow-up is advocated since most of the metastases are microscopic at the time of the diagnosis and malignancy is only declared years after the initial surgery, usually 5 to 15 years, sometimes even more [14]. Such a stringent and demanding monitoring risk of losing sight of a large number of patients operated on for a pheochromocytoma that is possibly malignant, exposing them to the risk of recurrence or metastases discovered at a non-curative stage making the prognosis of malignant pheochromocytoma uncertain.

4. CONCLUSIONS

The clinical and biological traits of malignant pheochromocytomas are identical to those of benign pheochromocytomas. The histological features remain non-discriminative. The only criterion for malignancy is the existence of metastases in a place exempt of chromaffin tissue, the infiltration or a locoregional recurrence. The evolution of malignant forms is often slow but unpredictable. The surgery should be as radical as possible. The Chemotherapy and the treatment with MIBG seem to control the disease in the long term. Patients' care requires a long-term monitoring and must integrate a multidisciplinary approach associating endocrinologist, surgeon, oncologist, radiotherapist and geneticist.

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