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A case report



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Multimodality imaging of bilateral pheochromocytoma. A case report

INTRODUCTION: *Bilateral pheochromocytomas (PHEO) are rare, often hereditary and linked to a germline mutation of RET, VHL or SDHx. They also occur sporadically.*

PRESENTATION OF CASE: *We report a case of a 76 year old female hospitalized for biological investigations following symptoms of abdominal discomfort with recurrent hypertensive episodes. The hormonal work up results favoured a diagnosis of a PHEO (urinary and plasma metanephrines > 10 times normal). Radiological investigations (CT-MRI): identified bilateral adrenal masses (47 mm in the right adrenal, 26 mm in the left adrenal). Functional imaging with 123 I-MIBG scintigraphy showed intense uptake in the right adrenal mass with limited uptake in the left, probably related to a fixation of the normal adrenal medulla. Due to the strong suspicion of bilateral PHEO, further imaging with an 18F-FDOPA PET was performed. This revealed intense hypermetabolism of the right mass but the left mass had similar metabolism to the liver, thought to be unsuspecting for a PHEO. It was decided to proceed with a laparoscopic right adrenalectomy. Hormonal investigations performed post-operatively revealed persistently elevated metanephrines. An 18F-FDG PET was performed, revealing an intense hypermetabolic focus in the left adrenal gland. A laparoscopic partial left adrenalectomy was subsequently performed 6 weeks after the initial right adrenalectomy.*

DISCUSSION AND CONCLUSIONS: *This case highlights the possibility of false negative results using specific functional imaging. In these situations, 18F-FDG PET may be useful. The MRI signal has an indisputable value. Until today, no germline mutation was found in this patient.*

KEY WORDS: Functional imaging, Germline mutation, Hypermetabolism, 18F-FDOPA PET/CT, 18F-FDG, 123 I-MIBG scintigraphy,

Introduction

Approximately 15% of adrenal incidentalomas occur bilaterally. While unilateral adrenal masses are benign in most cases, bilateral adrenal masses are more likely meta-

static disease, infiltrative disease, congenital adrenal hyperplasia, macronodular Cushing's syndrome or bilateral cortical adenomas ¹.

The incidence of bilateral pheochromocytoma (PHEO) is approximately 10% of cases (1) while its incidence in children is higher than in adults (20%) ².

PHEO is a catecholamine-secreting neuroendocrine tumor that originates in the adrenal medulla or in chromaffin tissues along the paravertebral sympathetic chain. Early diagnosis is critical for reducing mortality ^{2,3}.

Pheochromocytoma is reported to be genetically determined in 10-30% ⁴⁻⁶ and is commonly a component of hereditary endocrine syndromes including multiple endocrine neoplasia type 2 (MEN 2A and 2B), von Hippel-

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Lindau syndrome (VHL), much less frequently neurofibromatosis type 1 (NF1) and the pheochromocytoma-paraganglioma (PLG) syndromes related to mutations in one of the SDH genes (also called SDHx) ^{1,7,8}. In recent years four new genes (SDHA, SDHAF2, MAX, and TMEM127) have been identified as carrying a predisposition to PHEO-PGL syndrome ⁹.

Most cases of bilateral PHEO are hereditary ^{1,7} and are reported to develop in approximately 50% of MEN2A patients (within 10 years after unilateral adrenalectomy for PHEO) and in approximately 40-60% of VHL patients ⁷. The clinical symptoms of PHEO are related to catecholamine over-secretion and are characterised by sustained or paroxysmal elevations in blood pressure, headache, palpitations, pallor, profuse sweating and anxiety ¹⁰. We report a rare case of sporadic bilateral PHEO and we analyze the importance of multimodality imaging assessment.

Presentation of case

A 76- year-old female was presented to our Endocrine Surgery Unit with a two month history of feeling generally unwell with recurrent episodes of hypertension (diastolic > 120 mmHg) requiring hospitalization. Hormonal tests showed elevated plasma and urinary normetanephrines (measured twice) and Chromogranin A > 10 times the upper range limit.

Computed Tomography (CT) scan identified bilateral adrenal tumors (a heterogenous hypervascular mass of 47 x 34 mm diameter in the right adrenal and a homogenous mass with no hypervascular signs measuring 26 mm in the left adrenal). Three hepatic lesions were also identified of which the largest measured 15 mm in diameter (liver segments VII, VIII and IV respectively).

123 I-MIBG scintigraphy showed intense uptake in the right adrenal mass and limited uptake in the left adrenal, probably related to a normal adrenal medulla uptake. Uncertain increased uptake was also identified in liver

segment II. In the context of suspicious liver lesions, an MRI and additional functional imaging of the adrenals was performed.

MRI (Fig. 1 A, B) facilitated characterisation of the liver lesions as typical benign hemangiomas. Both adrenal lesions had heterogeneous enhancement consistent with the diagnosis of pheochromocytoma.

18F-FDOPA PET/CT (Fig. 2 A, B) was also performed and revealed intense hypermetabolism in the voluminous right adrenal mass, with a tumor SUV max of 4,6 g/ml, very suspicious of a pheochromocytoma. The left mass was unsuspecting, with similar metabolism to the liver. However, considering the strong suspicion of a bilateral pheochromocytoma, norcholesterol scintigraphy was performed to better characterize left adrenal mass, this did not demonstrate any hyperfixation suggestive of an adrenocortical lesion.

The case was discussed and radiological imaging reviewed at a multidisciplinary meeting and it was decided in the first instance to perform a laparoscopic right adrenalectomy. This procedure was performed without complication and the definitive histological examination was diagnostic of a pheochromocytoma, Pass score: 0.

In the post operative phase (day 10) a persistent elevation of circulating catecholamines was observed, with postoperatively urinary and plasma metanephrines eight times greater than normal and an 18F-FDG PET/CT was performed confirming an intense hypermetabolism in the left adrenal gland (SUV max Tumor 4,5, Sux max liver 2, Ratio 2,24 g/ml).

An octreotide scintigraphy (performed at day 15 post operative) was negative, not demonstrating any fixation in the left adrenal gland.

The patient proceeded to a laparoscopic partial left adrenalectomy. This procedure was performed without complication and again the definitive histological examination was diagnostic of a pheochromocytoma, Pass score: 0.

Postoperatively the patient was treated with hydrocorti-

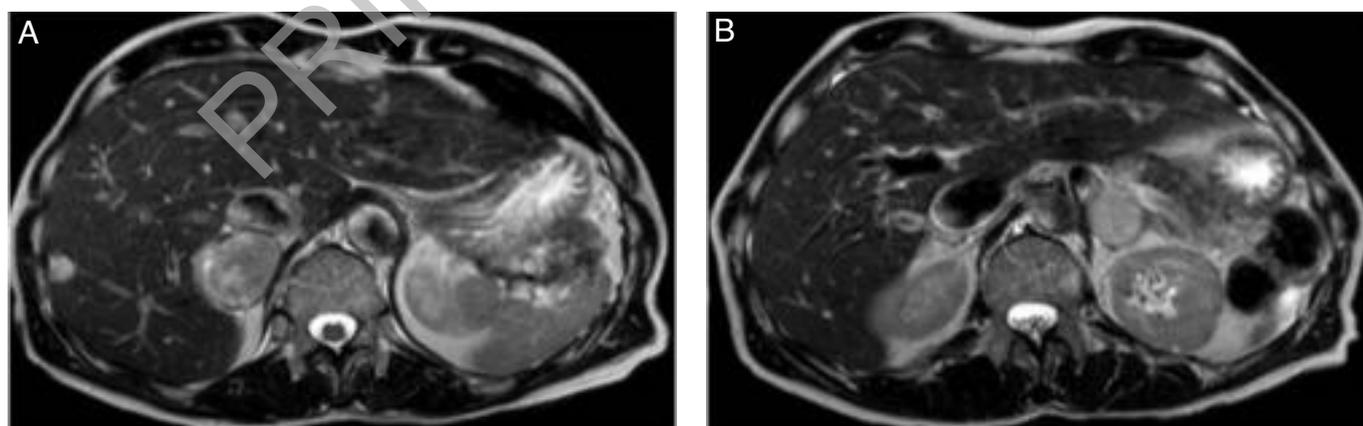


Fig. 1: (A, B) MRI: bilateral adrenal lesions with heterogeneous enhancement.

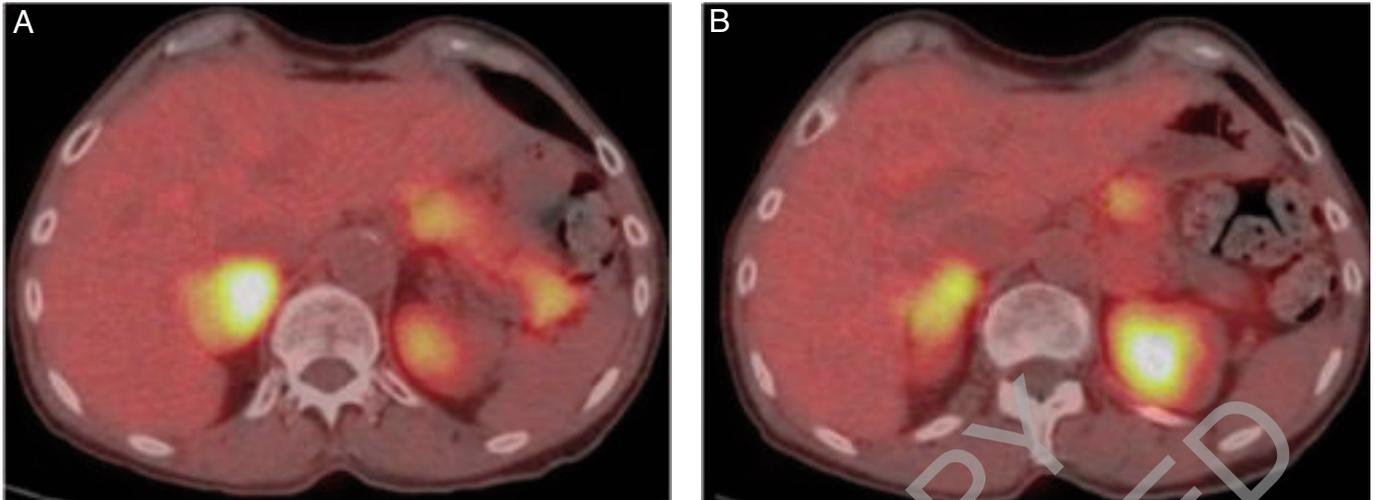


Fig. 2: (A, B) 18F- FDOPA: intense hypermetabolism in the voluminous right adrenal mass; tumour SUV max 4,6 g/ml. Absence of significant uptake in the left adrenal mass.

sone with a gradual withdrawal to a maintenance dose of 30 mg and 50 mg fludrocortisone daily. Genetic analysis did not identify germline mutation in the RET, SDHx and VHL genes.

Discussion

Diagnosis of pheochromocytoma is primarily biological consisting of identification of excessive secretion of plasma and urinary metanephrines which are more sensitive and specific than catecholamines^{2,10,11}. The measurement of plasma chromogranin A levels is also important but diagnostic specificity is quite poor according recent reports⁵. However once the biological diagnosis is established, characterization of the lesion with morphological and functional imaging is an essential component of the management strategy. The role of radiological investigations (CT and MRI) is indisputable for detecting adrenal or extra adrenal masses, and defining their characteristics and relationship with adjacent organs.

CT with evaluation of density (spontaneous and after injection of the contrast) and of contrast wash-out is considered a reliable technique. The study of density is capable of differentiating lesions with a reported sensitivity and specificity of up to 47%-71% and 100% respectively¹². PHEO and malignant lesions generally have a density of > 10 Hounsfield Units (HU), are heterogeneous, hypervascular and exhibit a reduced wash-out after 10 minutes¹³.

MRI has a sensitivity and specificity in tissue characterization of 78% and 87% respectively¹² and in our experience with this case it had an incontestable value; it identified bilateral PHEO and facilitated characterization of liver lesions.

I123-metaiodobenzylguanidine (MIBG) scintigraphy has been used for the evaluation of adrenal lesions for more than 25 years and today it remains the standard imaging procedure for identification of PHEO and/or PGL¹³⁻¹⁵. In conjunction with tomographic acquisition it has a reported 83-100% sensitivity and 85-100% specificity¹⁵; its sensitivity for detection of metastatic disease is about 65%¹⁶ and it appears sufficient to confirm a diagnosis of PHEO even in rare cases which are non-hyper-secreting³. Additionally MIBG scintigraphy has the advantage of whole-body screening. In our patient, MIBG demonstrated intense uptake in the right adrenal gland but left uptake was limited.

In this case the 18F-FDOPA PET/CT demonstrated a hypermetabolic signal in the right adrenal mass with an SUV max Tumor 4,6 g/ml, very suspicious of a PHEO and hypermetabolism in the left adrenal gland similar to the liver and thus unsuspecting for a PHEO although several studies have shown a good sensitivity equal or superior to MIBG scintigraphy in patients with PHEO and PGL^{17,18}. Until present, 18F-FDOPA false negative results have been reported in SDHx-mutated tumors¹⁹. In our experience, laparoscopic adrenalectomy was performed in two stages considered difficulties hormonal therapy replacement. In fact in patients undergoing bilateral adrenalectomy, glucocorticoid and mineralocorticoid cover is mandatory and the hemodynamic fluctuation are more pronounced and prolonged². No specific guidelines for optimal surgical approach exist¹.

The ideal operation in affected patients would be a partial adrenalectomy with removal of the medulla and preservation of the intact functional cortex^{7,20}.

After the first adrenalectomy, due to the persistent elevation of urinary and plasma metanephrines, an 18F-FDG was performed. Effectively 18F-FDG has the

advantage of using both qualitative and quantitative methods for the evaluation of adrenal masses²¹ and in this case it confirmed an intense hypermetabolism in the left adrenal gland with an SUV max tumor/SUV max liver ratio: 2,24 g/ml compatible with diagnosis of pheochromocytoma. It was based on these findings that the pre-operative diagnosis of a left pheochromocytoma was confirmed and a partial left adrenalectomy was performed. In our experience the combination of different and complementary imaging techniques enabled the diagnosis and management of a complex case within the multidisciplinary environment. The value of MRI and 18F-FDG in this case should be highlighted.

Conclusions

Bilateral PHEO management requires early diagnosis and rigorous management planning to reduce mortality and morbidity due to catecholaminergic charge²². A multidisciplinary team is essential to establish the best diagnostic workup.

In recent years due to advanced diagnostic techniques, the management strategy for PHEO has improved.

Multimodality imaging assessment is necessary to fully characterize adrenal lesions especially in the case of hyper-secreting lesions as in bilateral PHEO. The range of radiological investigations should be considered complementary. This case highlights the usefulness of functional imaging and emphasizes the concept that different techniques contribute differently to diagnosis and management.

In case of bilateral PHEO, surgical resection remains the treatment of choice but special care is needed to minimize the morbidity of adrenal insufficiency after bilateral adrenalectomy^{1,7}. When possible the operative strategy should be cortical-sparing adrenalectomy with minimal peripheral dissection of the cortex to prevent chronic corticosteroid replacement requirements⁷. Genetic screening should be performed routinely in these cases. Recent studies cite a total of 12 genes that play an important role in the pathogenesis of pheochromocytoma (RET, VHL, NF1, SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, TMEM127, MAX and HIF2a)⁶.

Riassunto

I feocromocitomi bilaterali sono rari; nella maggior parte dei casi presentano origine ereditaria e sono legati a mutazioni germinali relative ai geni RET, VHL o SDHx, tuttavia in altri casi non viene ritrovata alcuna eziologia. A tal proposito riportiamo il caso clinico di una donna di 76 anni, giunta alla nostra osservazione per malessere generale sopravvenuto in concomitanza di crisi ipertensive responsabili di ospedalizzazione. Il profilo ormonale realizzato in tale occasione, era suggestivo di feo-

cromocitoma (metanefrine plasmatiche ed urinarie 10 volte superiori al range di normalità).

Gli esami radiologici (TC e RMN) rivelavano due lesioni surrenaliche bilaterali di diametro rispettivamente a destra di 47 mm ed a sinistra di 26 mm.

Mentre la TC definiva le dimensioni di queste lesioni, il loro carattere eterogeneo e la loro ipervascolarizzazione oltre ai rapporti con gli organi adiacenti, la RMN si esprimeva già in favore di feocromocitoma bilaterale.

La scintigrafia alla MIBG mostrava una iperfissazione a carico della lesione surrenalica destra mentre sulla surrenale controlaterale evidenziava una fissazione limitata, relativa alla midollare normale. Tenuto conto del forte sospetto di feocromocitoma bilaterale, veniva eseguita una TEP alla 18F-FDOPA che mostrava un intenso ipermetabolismo a carico della massa surrenalica destra, mentre controlateralmente una fissazione simile a quella del fegato e pertanto non sospetta, nonostante molti studi sostengano una sensibilità uguale o addirittura superiore della TEP alla 18-FDOPA rispetto alla scintigrafia MIBG nei pazienti con feocromocitoma o paraganglioma.

In un primo tempo veniva eseguita una surrenalectomia destra per via laparoscopica. In fase post-operatoria, in seguito alla constatazione del persistente incremento delle metanefrine plasmatiche ed urinarie, veniva realizzata una TEP alla 18 FDG che confermava la presenza di un'area di ipermetabolismo intenso a carico della lesione surrenalica sinistra.

La TEP alla 18 FDG, grazie all'uso della metodica qualitativa e quantitativa nell'analisi della lesione, è stata molto utile nello svelarne la natura.

Veniva pertanto eseguita una surrenalectomia sinistra per via laparoscopica.

L'esame istologico per entrambe le lesioni era in favore di feocromocitoma, Pass score 0. Nella fase post-operatoria la paziente veniva trattata con idrocortisone a dosi decrescenti fino ad un dosaggio giornaliero di 30 mg in associazione a 50 mg di fludrocortisone.

Questo caso clinico dimostra ancora una volta la possibilità di falsi negativi da parte di tecniche di imaging funzionale specifiche. In questa esperienza, la TEP alla 18 FDG è stata molto utile. La RMN ha senza dubbio mostrato un valore incontestabile. In questa paziente non è stata trovata nessuna mutazione germinale a carico dei geni RET, VHL, SDHx.

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