Surgical treatment of pheochromocytoma in MEN 2

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Multiple endocrine neoplasia type 2 (MEN 2) is a rare autosomal dominant cancer syndrome. Forty to fifty percent of patients with MEN 2A develops pheochromocytoma. Surgeons treating these patients with pheochromocytoma have always been faced with question of whether to perform mono-or bilateral adrenalectomy and the timing of surgical intervention. Over the past 20 years, thanks to the development of ever more sophisticated techniques of diagnostic imaging (TC, MRI, Scintigraphy, PET), which make it possible to identify small lesions, and to ever more rapid laboratory tests, there has been a change in the surgical management of this condition. Surgeons moved from bilateral open adrenalectomy (6-9) to laparoscopic partial adrenalectomy and cortical sparing (10-13). After partial adrenalectomy one third of the patients require replacement therapy because the function of the residual parenchyma was compromised by excessive devascularization during surgery. In patients with bilateral pheochromocytoma it is advisable to perform only partial adrenalectomy of at least one gland, i.e. to completely remove the gland with the larger lesion and remove part of the gland with the smaller lesion to reduce the risk of recurrence. The authors report 4 cases of MEN 2, including 2 first-degree relatives, which illustrate the progress made in surgical treatment for pheochromocytoma.

KEY WORDS: Bilateral pheochromocytoma, Multiple endocrine neoplasia type 2 (MEN 2), Partial adrenalectomy

Introduction

Multiple Endocrine Neoplasia Type 2 (MEN 2) is a rare autosomal dominant cancer syndrome with an estimated prevalence of 1 in 30,000 individuals and is classified into three subtypes: MEN 2A, MEN 2B and familial medullary thyroid carcinoma (FMTC). Forty to fifty percent of patients with MEN 2A develops pheochromocytoma. Moreover, in 25% of cases mono- or bilateral pheochromocytoma is the initial presentation of MEN 2 [1-5]. Surgeons treating these patients with pheochromocytoma have always been faced with question of whether to perform mono-or bilateral adrenalectomy and the timing of surgical intervention [1-5]. Over the past 20 years, thanks to the development of ever more sophisticated techniques of diagnostic imaging which make it possible to identify small lesions (computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy and positron emission tomography (PET), and to ever more rapid laboratory tests, there has been a change in the surgical management of this condition. Surgeons moved from bilateral open adrenalectomy [6-9] to laparoscopic partial adrenalectomy and cortical sparing [10-13]. We report 4 cases of MEN 2, including 2 first-degree relatives, which illustrate the progress made in surgical treatment for pheochromocytoma.

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Case reports

CASES 1 AND 2

A.G, a 37-year-old white male, with a medical history of hypertension and a family history remarkable for MEN 2A, underwent total thyroidectomy with lymphadenectomy for medullary thyroid carcinoma. A TC of the abdomen revealed a 5cm lesion in the right adrenal gland and a 5.5cm lesion in the left adrenal gland (Fig.1). Scintigraphy showed increased uptake corresponding to the two lesions. The patient therefore underwent open bilateral adrenalectomy (Fig. 2). Histology confirmed pheochromocytoma.

D.G.,a 14-year-old white male, the son of A.G., underwent total thyroidectomy with lympadenectomy for medullary thyroid carcinoma. During follow-up abdominal ultrasound showed a 2.6 x1.6 cm hypoechoic and dishomogeneous mass in the right adrenal gland. An MRI confirmed the presence of two rounded masses in the right adrenal gland (2.6 cm and 1.0cm) (Fig. 3) and an 0.8 cm mass in the left adrenal gland. Meta-iodobenzylguanidine (MIBG) scintigraphy showed increased uptake only in the right adrenal gland. The patient underwent laparoscopic right adrenalectomy (Fig. 4). Approximately 2 years later, during careful monitoring of the left adrenal lesion, an increase in urinary catecholamine levels was noted, and MIGB scintigraphy showed increased uptake in the left adrenal gland . Therefore, laparoscopic partial left adrenalectomy was performed to remove the 1.2 cm mass (Fig. 5). Histology confirmed pheochromocytoma

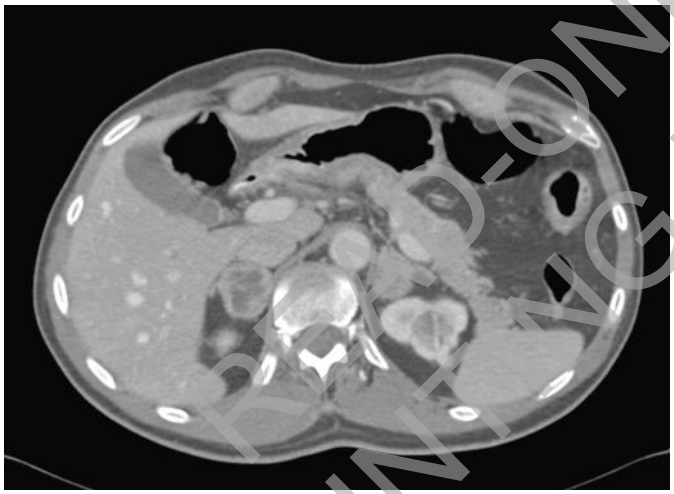

Fig. 1: TC scan of bilateral pheochromocytoma.

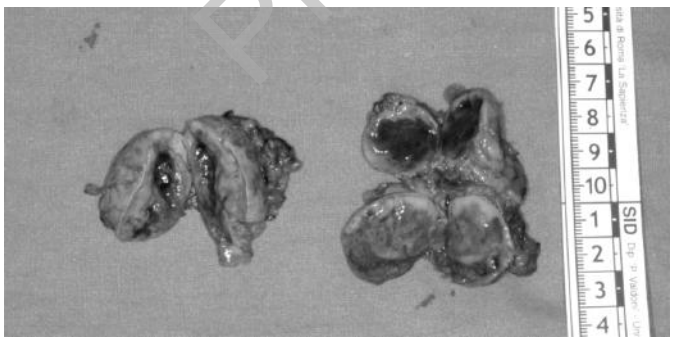

Fig. 2: Bilateral pheochromocytoma.

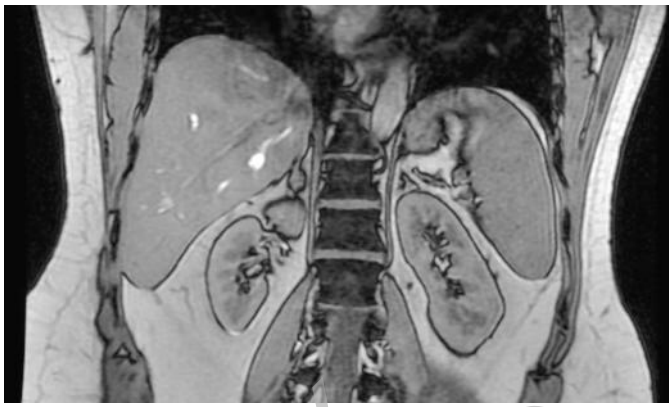

Fig. 3: MRI scan of right adrenal masses.

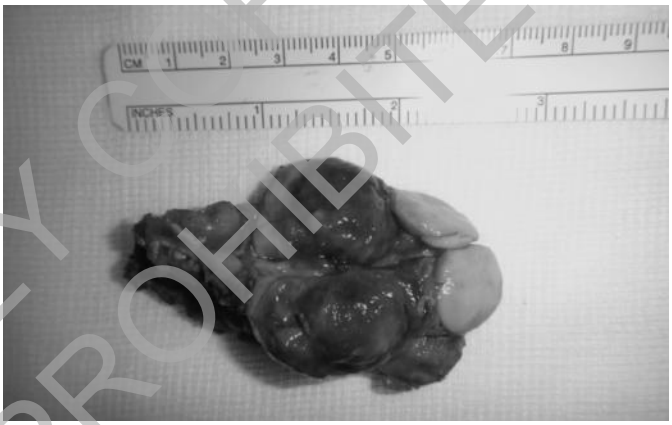

Fig. 4: Right adrenal masses

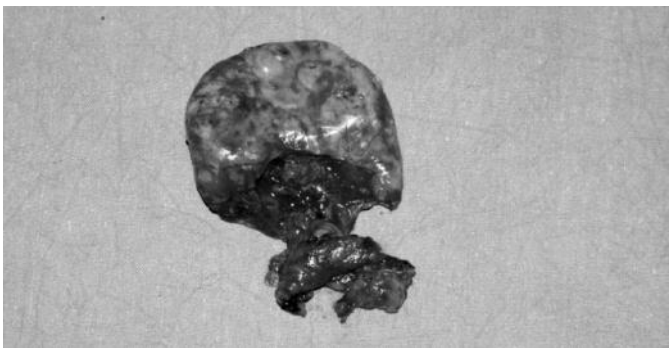

Fig. 5: Left partial adrenalectomy.

CASE 3

U.P. a 23-year-old white male, underwent total thyroidectomy for medullary thyroid cancer. After approximately one year he developed paroxysmal hypertension. TC of the abdomen revealed a 5cm lesion in the left adrenal gland. Therefore, the patient underwent left adrenalectomy via lumbotomy (Fig. 6). Approximately 1 year later. urinary catecholamine levels rose again and MRI showed a 2cm solid nodular mass in the right adrenal gland. Right adrenalectomy was performed via lumbotomy (Fig. 7). Histology confirmed pheochromocytoma in MEN2B.

CASE 4

C.C., a 38-year-old white female with MEN 2A syndrome, with a history of total thyroidectomy with lymphadenectomy for medullary thyroid cancer and laparoscopic right adrenalectomy for pheochromocytoma performed at another institution came to our attention for worsening symptoms of hypertension and an increase in urinary catecholamine levels. MRI revealed a 5cm nodular mass in the left adrenal gland (Fig. 8). Due to the size and morphology of the tumor the patient underwent laparoscopic left adrenalectomy (Fig. 9). Histology confirmed pheochromocytoma.

Fig. 6: Left adrenal gland.

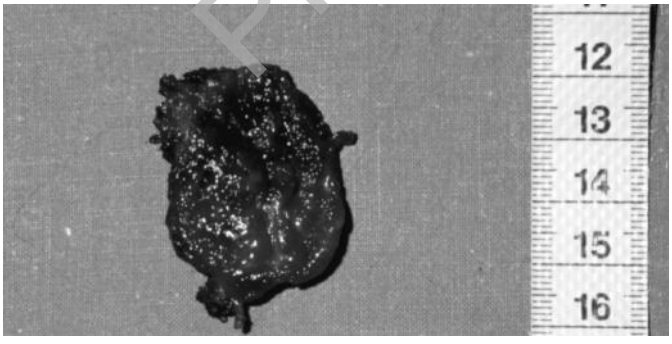

Fig. 7: Right adrenal mass.

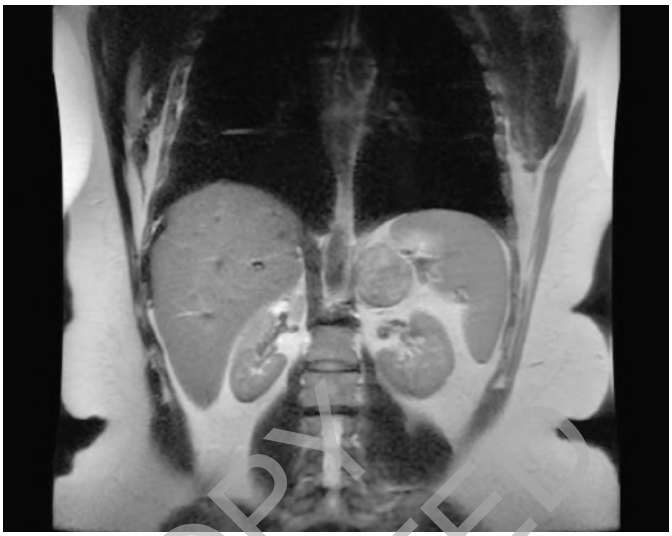

Fig. 8: MRI scan of left adrenal mass.

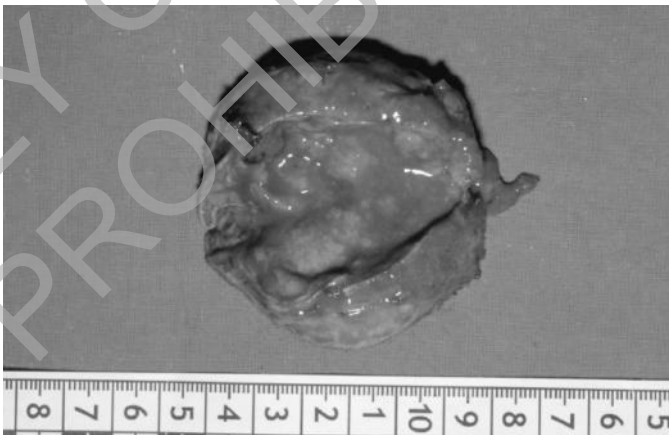

Fig. 9: Left adrenal pheocromocytoma.

Discussion

Surgical management of pheochromocytoma in MEN 2 patients has been a matter of debate since Sipple first described an association of thyroid cancer with pheochromocytoma in 1961. The incidence of pheochromocytoma in MEN 2 ranges from 40-50%. The rarity of this genetic syndrome (approximately 1/30,000 individuals affected) explains why the literature on MEN 2 consists mainly of reports of single cases or small series, a number of patients so limited that clear treatment guidelines cannot be established [1-5].

Because of the great leap forward made in diagnostic imaging (CT, MRI, scintigraphy and PET) it possible to study both the morphology and function of the adrenal glands with great precision and to identify the MEN 2 syndromes, and thus the adrenal lesions associated with them, much more quickly .

The discovery and use of new drugs (alpha blockers, beta blockers, calcium antagonists, and catecholamine synthesis inhibitors) has improved patient management and made possible optimal timing of surgery.
Until the 1990s routine bilateral adrenalectomy was performed when lesions were larger than 5 cm, even in cases of unilateral disease in order to prevent recurrence or persistent disease in remnant adrenal tissue. However, the patient is then at risk of Addison's syndrome which is associated with significant morbidity and mortality and requires lifelong steroid replacement therapy which is not easily maneagable, even in specialized centers. There is also the risk of negative repercussions on the patient's quality of life due to overtreatment with steroids (with results such as obesity, diabetes, and osteoporosis) or undertreatment [14,15]. From open bilateral adrenalectomy [6-9], surgeons moved on to laparoscopic unilateral adrenalectomy followed by surveillance of the remaining adrenal gland, and then to partial uni- or bilateral adrenalectomy sometimes performed with new, sophisticated techniques that include cortical sparing.[10-13]
The knowledge that the risk of pheochromocytoma developing in the contralateral adrenal gland is 30% at 5 years and 50% at 11 years has played a key role in determining the current preference for treating only the affected gland [15,16,18]. In cases of surgery performed on the remaining adrenal gland after a primary unilateral adrenalectomy, it seems logical that partial adrenalectomy should be the preferred treatment.
Partial adrenalectomy is actually better suited for the treatment of aldosterone producing adenomas [19-21] because in the case of pheochromocytoma the dimensions of the tumor mass (usually <3cm) and its location in the gland (peripheral or central) as well as the position of the adrenal vein. If the tumor is peripherally located, there is better venous drainage from the stump after resection and thus more chance of residual postoperative function. Although venous drainage from the adrenal medulla is achieved mainly via the central adrenal vein some authors have demonstrated good residual adrenal function even after partial bilateral adrenalectomy without preservation of the central adrenal veins [11,19] Recurrence after partial adrenalectomy, reported in 10-20% of cases, does not exclude reintervention [11,19]. From a purely technical point of view it is necessary to determine the exact resection margins (0.3-0.5cm), the location of the tumor mass, and its size.
It is important not to underestimate studies indicating that even after partial adrenalectomy one third of the patients require replacement therapy because the function of the residual parenchyma was compromised by excessive devascularization during surgery [5,16-18] Moreover, the incidence of disease in the remaining adrenal gland is the same after total and after partial unilateral adrenalectomy [5,16-18].
In conclusion, in patients with bilateral pheochromocytoma it is advisable to perform only partial adrenalectomy of at least one gland, i.e. to completely remove the gland with the larger lesion and remove part of the gland with the smaller lesion to reduce the risk of recurrence [12,19,22-28].

Riassunto

La MEN 2 è una rara malattia autosomica dominante con incidenza di 1 su 30.000 nati circa che presenta in una percentuale alta (40-50%) di casi il feocromocitoma che in un quarto dei casi può rappresentare la malattia d'esordio. Il trattamento chirurgico del Feocromocitoma nei casi di MEN 2 è sempre stato motivo di grande discussione tra i chirurghi a partire dalla prima descrizione di Sipple nel 1961, ponendo al chirurgo il problema sulla tipologia di intervento da eseguire, surrenectomia mono o bilaterale, e sul "timing" dell'intervento. Il grande balzo in avanti delle tecniche di immagine (TC, RM, scintigrafia e PET) permette di studiare con precisione, sia morfologicamente che funzionalmente, le ghiandole surrenaliche ottenendo un più rapido riconoscimento delle sindromi stesse e quindi di lesioni surrenaliche iniziali. La scoperta e l'utilizzazione di nuovi farmaci (alfa - beta bloccanti, calcio antagonisti e inibitori della sintesi delle catecolamine) permettono un miglior controllo medico del paziente e permettono attualmente di scegliere il corretto "timing" chirurgico. Da interventi bilaterali in chirurgia aperta , si è arrivati ad interventi laparoscopici parziali e "cortical-sparing". Fino agli anni '90 la surrenalectomia bilaterale di principio era eseguita anche nei casi di lesione monolaterale ed in presenza di grandi masse superiori a 5 cm al fine di prevenire le recidive o i residui. Tale approccio esponeva però il paziente ad una possibile sindrome di Addison con riconosciuta mortalità e morbilità oltre che alla necessita di una terapia sostitutiva a vita. Dalla surrenalectomia bilaterale laparotomica si è passati alla monolaterale con tecnica laparoscopica con follow-up del surrene controlaterale, per giungere alle surrenalectomie parziali mono o bilaterali che includono anche tecniche più sofisticate di asportazione della midollare del surrene con conservazione della corticale. Da non sottovalutare inoltre che dopo surrenalectomie parziali, in un terzo dei casi, si deve ricorrere ugualmente a terapia sostitutiva, per mancata funzionalità del parenchima residuo per eccessiva devascolarizzazione avvenuta durante l'intervento chirurgico. Nel feocromocitoma bilaterale è consigliabile eseguire una surrenalectomia parziale in almeno una ghiandola, asportando il surrene con la lesione maggiore ed eseguendo una surrenalecectomia parziale nel lato con lesione più piccola in modo da ridurre il rischio di recidive. Nel lavoro viene riportata una serie di casi, anche famigliari, di MEN 2 nei quali si può notare l'evoluzione del trattamento chirurgico.

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