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Pheochromocytoma: More than a decade of experience. Review of the literature

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A B S T R A C T

Objectives: We present 18 patients with pheochromocytoma in the past 12 years.
Material and methods: It is a retrospective observational study evaluating the most important clinical, biochemical and pathological aspects.
Results: The mean age was 53.5 years with male predominance and monitoring of five years, the most frequent being incidental findings (29%). Four patients had a hereditary familial syndrome.

The tumors were equally distributed with a bilateral case. For the clinical study plasma catecholamines and metanephrines in urine for 24h were requested a and subjected to control blood pressure before surgery and beta blockers.

Until the introduction of laparoscopic surgery in our department in 2003, the treatment of choice was open surgery. Transabdominal subcostal access was more frequent (47%) and average duration of 207min.

No patients showed metachronous tumors and two patients developed distant metastases to death in short time.
Conclusions: Pheochromocytoma is a threatening disease due to its cardiovascular morbidity, which requires an analytical and functional study.

Surgical treatment, by open or laparoscopic surgery, depending on the characteristics of the tumor and the patient, has satisfactory and comparable results.

Feocromocitoma: más de una década de experiencia. Revisión de la literatura

Palabras clave:
Feocromocitoma
Laparoscopia

R E S U M E N

Objetivos: Presentamos 18 pacientes diagnosticados de feocromocitoma en los últimos 12 años.
Material y métodos: Es un estudio retrospectivo observacional valorando los aspectos clínicos, analíticos y patológicos más importantes.

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Suprarrenal
Hipertensión arterial

Resultados: La edad media fue de 53,5 años con predominio masculino y un seguimiento de 5 años; siendo la consulta más frecuente el hallazgo incidental (29%). Cuatro pacientes padecían un síndrome familiar hereditario.

Los tumores se distribuyeron por igual con un caso bilateral. Para el estudio clínico se solicitaron catecolaminas y metanefrinas plasmáticas y en orina de 24 h, siendo sometidos a control de la tensión arterial antes de la cirugía con alfabloqueantes y betabloqueantes.

Hasta la introducción de la cirugía laparoscópica en nuestro servicio en el 2003, el tratamiento de elección era la cirugía abierta. El acceso transabdominal subcostal fue el más utilizado (47%) y la duración media de 207 min.

Ninguno presentó tumores metacrónicos y dos pacientes desarrollaron metástasis a distancia con fallecimiento en corto espacio de tiempo.

Conclusiones: El feocromocitoma es una enfermedad amenazante por su morbilidad cardiovascular, que precisa realizar un estudio analítico y funcional.

El tratamiento quirúrgico, por vía abierta o laparoscópica, dependiendo de las características del tumor y del paciente, tiene resultados satisfactorios y comparables.

Introduction

Pheochromocytoma is an uncommon condition which has attracted the attention of researchers and clinicias, who have cooperated over time to find effective disease detection, location, and management methods. However, diagnosis and treatment of this condition continue to represent a challenge because increasingly common use of imaging tests may lead to an increased detection of incidental renal masses.[1]

Pheochromocytomas are catecholamine-secreting tumors arising from the neuroectodermal tissue of neural crest. Seventy percent of chromaffin cells from neural crest will eventually form the adrenal medulla, and 15% the paragangloinic system, consisting of carotid bodies (chemodectomas) and aortic bodies (between diaphragm pillars and renal pedicles), the Zuckerkandl organ (between the inferior mesenteric artery and aortic bifurcation), and other remnants housed along the sympathetic ganglionar chain (paragangliomas). More uncommon locations include the bladder, lung hilum, and intracranial areas.[2]

We report our experience with this condition, which requires a multidisciplinary diagnosis, as shown by the data. However, definitive curative treatment is merely surgical and is thus, in our view, part of standard urological practice, as all other adrenal surgical procedures.

Materials and methods

A retrospective, observational study was conducted in 18 patients diagnosed with pheochromocytoma who underwent surgery at the Complejo Hospitalario Universitario de Albacete from January 1, 1997 to December 31, 2009.

Demographic, clinical, and pathological data were collected from their clinical records.

Patients were referred to our department from other departments of the same hospital complex. Open or laparoscopic surgery was performed. After hospital discharge, patients were seen at the urology outpatient clinic and at the referring department.

A descriptive study was conducted using measures of central tendency and dispension for quantitative variables and percentages for qualitative variables. SPSS 15.0 software was used for statistical analysis.

Results

Mean patient age was 53.6 years, and male:female ratio was 2:1. Mean patient follow-up was 5.4 years (range, 0.01-11.81 years; SD 3.97). Patients were referred by the nephrology (6 patients), endocrinology (6), internal medicine (3), pneumonology (2), and ICU (1) departments.

Pheochromocytoma occurred in four patients in the setting of a multiple endocrine neoplasia (MEN IIA), and in one patient with von Hippel-Lindau syndrome.

Incidentaloma was the most common reason for consultation (29.4%), followed by sustained HBP (high blood pressure) (23.5%). Other reasons included paroxysmal HBP (17.6%), weight loss (11.8%), headache (5.9%), and tachycardia associated to the above symptoms.

The initial imaging test performed was computed tomography (CT) in 13 patients and magnetic resonance imaging (MRI) in four patients. A metaiodobenzylguanidine (MIBG) scan was also requested in seven patients.

Tumors were equally distributed in both adrenal glands, and bilateral tumors were found in one patient. A metachronous pheochromocytoma occurred in one patient five years after undergoing surgery in the contralateral adrenal gland at another center.

Metanephrine and catecholamine levels were measured in plasma and 24-hour urine. Norepinephrine and epinephrine levels in 24-hour urine were higher than the reference values in 70% and 50% of patients respectively.

The clonidine test was done in a single patient, with a positive result.

Before surgery, blood pressure was treated in all patients with alpha-blockers (phenoxybenzamine 20-120 mg/24 h) for a mean of 14 days (range, 7-21 days). No adverse effects occurred during administration. In eight patients, β-adrenergic blockade with propanolol or atenolol was required before surgery and after α blockade.

Open surgery was the procedure of choice (76%) until laparoscopy was introduced in our department. A subcostal transabdominal approach was most commonly used (47%), followed by a posterior lumbar approach (24%). A median laparotomy was performed in a single patient. Mean operating time was 256 min range, 185-420 min). In laparoscopic procedures, mean operating time was 107 min (range, 50-240 min). This difference may be explained by the smaller size of tumors for which laparoscopy was used.

Median peroperative bleeding was 560 mL. Six patients required transfusion during the early postoperative period. One of these experienced during surgery massive bleeding from a large lesion in the right side invading adjacent structures which caused death in the early postoperative period. Mean hospital stay was 11 days (range 4-35 days; SD, 8.5).

Fifty-eight percent of patients experienced at least one hypertensive episode (blood pressure >160/90 mmHg) but no more than seven during surgery. Episodes were treated with nitroprusside, nitroglycerin, uradipil, nifedipine, or esmolol. Forty-one percent of patients experienced at least one episode of arerial hypotension (blood pressure <80-45 mmHg) (range, 1-9). Such episodes were managed with norepinephrine, epinephrine, dopamime, or volume replacement.

Mean largest tumor diameter was 6.5 cm (range, 1.8-10 cm; SD, 2.77), while mean tumor weight was 93.6 g (range, 9.0–280 g; SD, 84.19). Coexistence of a metastasis from renal carcinoma and pheochromocytoma (collision tumor) was reported in one patient, and a compound pheochromocytoma (consisting of pheochromocytoma and ganglioneuroma) was found in another patient.

Four patients experienced postoperative complications consisting of hospital-acquired infection (1), surgical wound infection (1), respiratory distress (1), and retroperitoneal abscesss (1) leading to ICU admission and subsequent death.

Afer surgery, five patients continued to have sustained HBP but required lower drug doses for control. Distant metastases (in the liver and bones) occurred in two patients, who died shortly afterwards.

Discussion

Pheochromocytoma is a disease whose diagnosis and treatment continue to represent a challenge. Its incidence ranges from 0.8 and 2 cases/100,000 inhabitants/year. The condition occurs between the fourth and sixth decades of life and shows a very slight predominance in females, although this was not seen in our series.[3]

Pheochromocytoma occurs as an isolated, sporadic condition in up to 90% of cases, but the remaining 10% occur as part of familial syndromes inherited as autosomal dominant disorders, including multiple endocrine neoplasia type 2 (MEN-2) with the variety 2A or Sipple syndrome (medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism), and form 2B (medullary thyroid carcinoma, pheochromocytoma, presence of neurons, and Marfan-like habitus with occasional gastrointestinal ganglioneuromas). Other familial syndromes include von Hippel-Lindau disease (1/36,000), where 10%-20% develop (bilateral) pheochromocytomas, multiple paraganglionic syndromes, and Carney syndrome (gastric leiomyosarcoma, pulmonary chondroma, and functioning extra-adrenal pheochromocytoma). Consideration should finally been given to neurofibromatosis type I or von Recklinghausen's disease, which may occur with pheochromocytoma in 2% of cases (20% bilateral), cutaneous neurofibroma, "café au lait" spots in skin, optic glyoma, benign hamartoma of the iris (Lisch nodule), bone dysplasia, macrocephaly, growth retardation, and cognitive disorders.[4] Non-familial syndromes include Bourneville-Pringle tuberous sclerosis.

Malignant pheochromocytomas account for 10%-25% of cases and are characterized by bone, lung, liver or splenic metastases, secreting other metabolites such as dopamine. Five percent of these occur during follow-up, particularly in extra-adrenal tumors (30%-40%), in those greater than 6 cm secreting dopamine only and when HBP persists after surgery. Recurrence occurs at between 5 and 6 years, and treatment is based on resection, adrenergic blockade, and chemotherapy with cyclophosphamide, vincristine, and dacarbazine in non-resectable tumors.[4] Mean survival is 80 months.

Initial clinical signs are variable and usually related to high blood pressure (HBP) (0.1%-1% of hypertensive population). Approximately 10% of patients have no or mild HBP, which makes laboratory confirmation indispensable. Levels of catecholamines and their metabolites should be measured in urine and blood, and will be elevated in 95%-99% of patients.[5] Catecholamines (total and fractionated) and metanephrines should first be measured in 24-hour urine, which should be acidified during collection to maintain a pH less than 3 and stored cold. If these tests are not diagnostic, plasma metanephrines must be measured. In the event of doubt, the phentolamine suppression, clonidine, or glucagon tests may be used. We have used the clonidine test in one patient with a positive result, as this substance was not able to suppress plasma norepinephrine levels, as should occur under normal conditions due to stimulation of alpha-adrenergic receptors.

Imaging tests also play an essential role in diagnosis; both CT and MRI (especially with contrast) are the most precise method to reveal pheochromocytoma.[6]

A CT scan (Figure 1A) is the most commonly used test, having a diagnostic efficacy of 89%-96% and a 90% resolution for lesions greater than 1 cm in size, but use of intravenous contrast may cause a crisis. MRI (Figure 1B) (99% sensitivity, 88% specificity) provides greater resolution for extra-adrenal masses and for the study of extension or involvement of major vessels. An additional imaging test available for more than 15 years but not routinely used is a scan with metaiodobenzylguanidine (MIBG) labeled with ^{123}I and ^{131}I, which allows for detecting adrenal and extra-adrenal tumors or metastases with 80%-85% sensitivity and 88%-100%

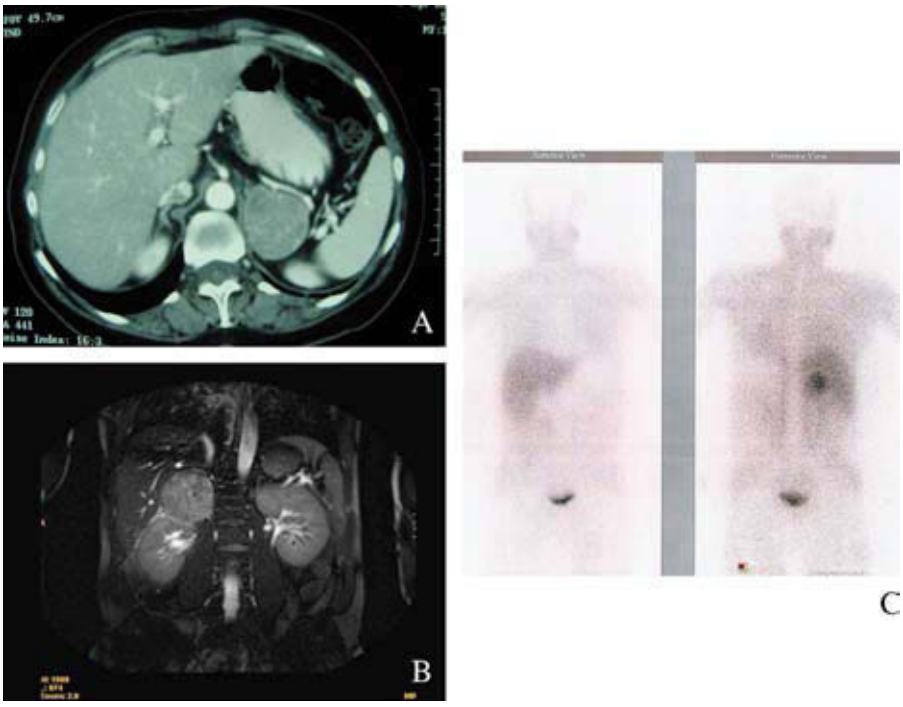

Figure 1 – A) CT image of a left adrenal mass. B) MRI showing a left pheochromocytoma lesion. C) Adrenal metaiodobenzylguanidine scan.

specificity (Figure 1C).[7] Its disadvantages include radiation, high cost, poor anatomical definition, and the need for prior iodine administration to prevent negative effects on the thyroid gland.

Thyroid and parathyroid examination is sometimes required because of the potential associations with thyroid carcinoma and hyperparathyroidism.

Agents such as halothane or cyclopropane should not be used for anesthesia because they may cause ventricular arrhythmia. Patients with pheochromocytoma have permanent vasoconstriction, and adequate volume replacement therapy should therefore be administered with the appropriate prior drug treatment. Adequate alpha-adrenergic blockade before surgery decreases intraoperative and postoperative complications. While use of specific alpha-blockers or alpha-1 antagonists varies depending on the center, recent studies support use of phenoxibenzamine because it is irreversible and non-specific.[8]

Surgery for pheochromocytoma consists of complete tumor excision, minimal handling before ligation of the main venous drainage, which is initially controlled when possible, adequate hemostasis, and prevention of dissemination in malignant cases. There are multiple approaches for adrenal gland surgery, including posterior extraperitoneal, posterior transpleurodiaphragmatic, posterolateral retroperitoneal (the approach most familiar to urologists), thoracophrenolaparotomy, and anterior transperitoneal (the one most commonly used by us) approaches. They all are intended to find a suitable surgical field that allows for gland visualization and dissection in a craniocaudal direction with no traction, excising the complete tumor with its capsule and surrounding connective tissue (Figure 2A and B).[9]

Although pheochromocytoma has traditionally been a relative contraindication for laparoscopy because of the theoretical risk of catecholamine discharge triggered by manipulation, several studies have shown this to be a safe and effective approach providing the same benefits as in all other adrenal conditions (less intraoperative stress, morbidity, and pain). The main difficulty lies in the handling of large tumors, and laparoscopy is therefore reserved for tumors less than 6 cm in size, although excision of tumors up to 12 cm in size have been reported in literature.[10] Our mean time using the laparoscopic transperitoneal approach was shorter than in the reported series, although it clearly depends on tumor size (Figure 2C and D).

The most common complications after surgery for pheochromocytoma include hypoglycemic episodes and hypotension, which is not usually severe. Postoperative hypertension is due to fluid overload or incomplete resection, and up to 25% of patients have essential hypertension after surgery, a proportion very similar to that found in our series.

Patient follow-up consists of measurement of urine and plasma catecholamine levels in the month subsequent to surgery. In familial syndromes, annual blood pressure and catecholamine monitoring for at least five years is indispensable because of the potential occurrence of metachronous tumors.[11]

Conclusion

Pheochromocytoma is a rare, life-threatening disease whose classical clinical signs include hypertension, sweating, palpitations, and headache.

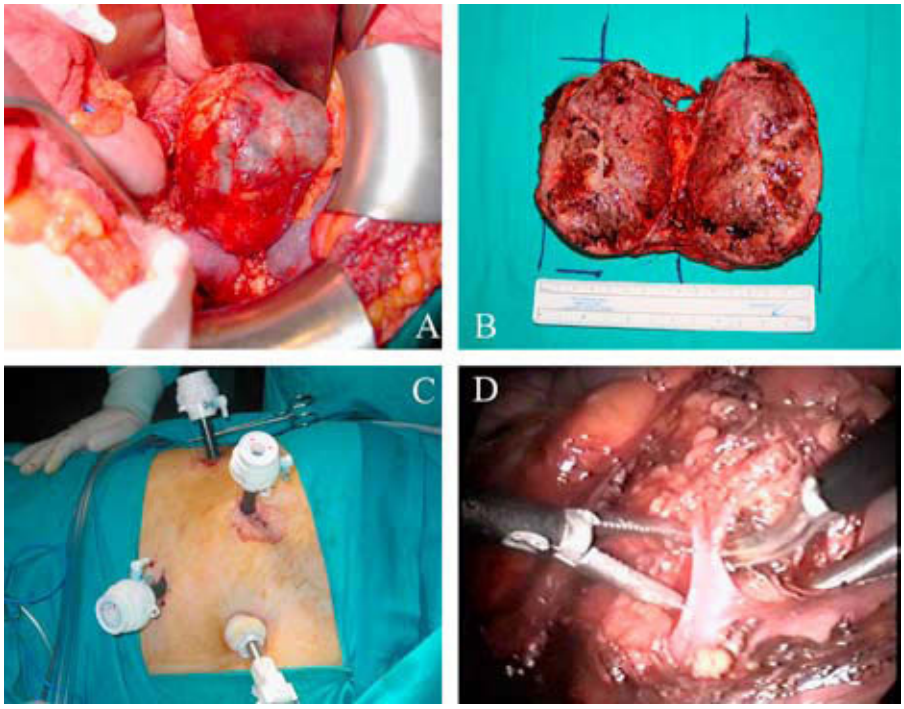

Figure 2 – A) and B) Images of open surgery for pheochromocytoma. View in the surgical field and gross examination. C) and D) Laparoscopic adrenal surgery. Trocar placement (C) and suprarenal vein dissection (D).

Surgical excision following preoperative preparation is the treatment of choice and cures pheochromocytoma in sporadic cases. However, pheochromocytoma occurring in the setting of a familial syndrome requires a close, long-term follow-up because of its greater chance of recurrence.

There are multiple open surgical approaches for treating this condition, but laparoscopic adrenalectomy is effective and safe as first alternative for selected small tumors.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Young WF. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med. 2007;601-10.
2. Gimenez Bachs JM, Salinas Sánchez AS, Lorenzo Romero JG, Segura Martin M, Hernández Millan I, Barba Romero MA, et al. Feocromocitoma del órgano de Zuckerkandl. A propósito de un caso. Actas Urol Esp. 2002;26:372-6.
3. Yu R, Nissen NN, Chopra P, Dhall D, Phillips E, Wei M. Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. Am J Med. 2009;122:85-95.
4. Thompson GB. Pheocromocitoma in MEN 2A, MEN 2B and von Hippel. Lindau disease "in" Adrenal glans diagnostic aspects and surgical therapy. New York; 2005.
5. Eisenhofer G, Keiser H, Friberg P, Mezey E, Huynh TT, Hiremagalur B, et al. Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. J Clin Endocrinol Metab. 1998;83:2175-85.
6. Salinas Sánchez A, Lorenzo Romero J, Segura Martin M, Hernández Millan I, Pastor Guzman J, Virseda Rodríguez J. Patología suprarrenal quirúrgica. Experiencia de 10 años y Revisión de la literatura. Arch Esp Urol. 1998;51:227-40.
7. López Ferrandis J, Saiz Sansi A, Cervera Delgado M, Rioja Zuazu J, Regojo Balboa JM, Berian Polo JM. Feocromocitoma con trombo en cava. Actas Urol Esp. 2005;29:281-6.
8. Pacak K. Approach to the patient. Preoperative Management of the Pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92:4069-79.
9. Virseda Rodríguez JA, Salinas Sánchez AS, Hernández Millán I. Casado Moregón L. Diagnóstico y tratamiento de los tumores suprarrenales "en" tratado de Oncología Urológica; 2003, cap. 34 p. 447–460.
10. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg. 1997;226:238-46. discussion 46–7
11. Reckler JM, Vaughan ED, Tjeuw M, et al. Pheochromocytoma "in" Adrenal Disorder. Ed. Carey R.M Thieme Medical Publishers Inc.; 1989. p. 259–279.