CASE REPORT

Laparoscopic adrenalectomy as an effective approach to massive bilateral pheochromocytomas

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SUMMARY

Pheochromocytomas are catecholamine-secreting neoplasms, arising from adrenomedullary chromaffin cells. In type 2 multiple endocrine neoplasia (MEN2) syndrome, pheochromocytomas are usually benign but with predisposition to be bilateral (50%–80% of cases). The authors present the case of a young patient diagnosed with uncommonly large bilateral cystic pheochromocytomas and simultaneous detection of medullary thyroid carcinoma. Molecular testing confirmed germline *RET* codon C634 mutation, consistent with MEN2A syndrome. The patient underwent bilateral laparoscopic adrenalectomy plus total thyroidectomy with central lymph node dissection without associated complications. The histopathological study of the surgical specimens revealed bilateral benign pheochromocytomas (Ki67 of 2%) and a medullary carcinoma of the thyroid T1bN0M0; R0, respectively. One year after surgery, the patient was considered free of disease.

This case demonstrates that bilateral laparoscopic adrenalectomy can be a safe and feasible approach for pheochromocytomas in MEN2 syndrome, even in lesions with large diameter. However, due to elevated possibility of recurrence, patients should maintain lifelong follow-up.

BACKGROUND

Pheochromocytoma is a rare catecholamine-secreting neoplasm arising from chromaffin cells in the adrenal medulla, with an estimated annual incidence of 2–8 per million.^{1,2}

Bilateral pheochromocytomas are usually observed in the context of specific syndromes, namely type 2 multiple endocrine neoplasia (MEN2), von Hippel-Lindau (VHL) syndrome or neurofibromatosis type 1 (NF1).³ In MEN2 syndrome, pheochromocytoma is the first clinical manifestation of the disease in 25% of cases, being diagnosed after medullary thyroid carcinoma (MTC) in 40%. In 35% of cases MTC and pheochromocytoma are diagnosed at the same time.^{4,5}

Currently, laparoscopic adrenalectomy is the preferred surgical approach for pheochromocytoma in patients with MEN2, being the rate of conversion to laparotomy less than 10%.⁶ Despite that the benefits of unilateral laparoscopic adrenalectomy are well recognised, the outcomes of bilateral laparoscopic adrenalectomy are still under debate.

The authors present a case of a young patient with MEN2A syndrome and confirmed *RET* proto-oncogene mutation at codon 634 TCG>TGG

(C634W), with large bilateral pheochromocytomas, concurrently diagnosed with MTC. Before undergoing total thyroidectomy with central lymph node dissection, the patient was submitted to bilateral laparoscopic adrenalectomy, which was uneventful, demonstrating that this procedure may be considered a safe and feasible approach for bilateral pheochromocytomas in MEN2 syndrome.

CASE PRESENTATION

A 19-year-old female patient presented to the emergency department with recurrent episodes of palpitations, headache, nausea and abdominal discomfort that had begun 2 years before. Because of persistent abdominal pain, an abdominal ultrasound study was performed, having showed ‘bilateral cystic perirenal lesions’; after that, abdominal CT confirmed the presence of ‘two cystic multiseptated formations, in the dependence of the adrenal glands, on the right with 11.3 cm and on the left with 7.8 cm larger diameter, without infiltrative aspects or evidence of suspicious abdominal lymph nodes’ (figure 1).

The patient had no relevant personal or family medical history.

INVESTIGATIONS

The patient was admitted to complementary workup that revealed marked elevation of plasma-free metanephrines, urinary metanephrines higher than 25 000 µg/24 hours (25–312), elevation of vanillylmandelic acid (VMA) and calcitonin. The parathyroid hormone (PTH) assay was normal, as well as the remaining blood tests performed (table 1).

The thyroid echography showed a hypoechoic nodule with 1.1 cm larger diameter, in the middle of the left lobe, with ill-defined limits and one microcalcification. There was no evidence of cervical lymphadenopathies. Fine-needle aspiration biopsy was performed and the cell-block and immunohistochemistry study presented a result compatible with medullary thyroid carcinoma. Owing to the previous result, a cervical-thoracic CT was performed, confirming the presence of a thyroid nodule on the left lobe, with larger diameter of 1.1 cm, without evidence of other cervical expansive formations or lymphadenopathies in the hilar and mediastinal areas.

Abdominal MRI was also performed and demonstrated two bulky masses in adrenal glands, the right with 10.8 cm and the left with 7.8 cm, well defined,

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Figure 1 Abdominal CT scan, with contrast: coronal and axial axes.

with multicystic areas. Both kidneys were diverted inferiorly and adjacent organs had no signs of intrusion.

In addition, ¹²³I-metaiodobenzylguanidine scintigraphy showed the presence of massive bilateral pheochromocytomas and abnormal fixation on the topography of the left thyroid lobe (figure 2).

Finally, molecular genetic testing showed a germline *RET* proto-oncogene mutation at codon 634 TCG>TGG (C634W), consistent with the diagnosis of MEN2A. Genetic screening of family members (parents and sister) was also performed and showed a negative result.

TREATMENT

After complementary diagnostic evaluation, the patient started α -adrenergic and then β -adrenergic blockade (fenoxibenzamine 10mg twice daily plus propranolol 10mg twice daily), with adequate clinical response (systolic blood pressure <140 mm Hg; diastolic blood pressure <90 mm Hg; heart rate <100 bpm)

Table 1 Laboratory assays in the first evaluation of the patient

Analyte	Result	Reference value
ACTH pg/mL	14	9–52
Cortisol μ g/dL	14	5–25
Free urinary cortisol μ g/24 hours	31	10–80
Cortisol (low dose dexamethasone suppression test) μ g/dL	1.4	–
TSH μ UI/mL	4.8	0.4–4.0
T4L ng/dL	0.9	0.8–1.9
PTH pg/mL	41	9–72
25-OHD ng/mL	36	>29
Calcitonin pg/mL	55	<10
Plasma-free metanephrine pg/mL	7386.4	<60
Plasma-free normetanephrine pg/mL	8057.8	<20
Urinary metanephrines μ g/24 hours	25 179.75	25–312
Vanilmandelic acid mg/24 hours	57.35	<7.0
CEA ng/mL	6.5	<5.4
DHEA-SO4 μ g/mL	0.7	0.35–4.3
Androstenedione ng/mL	2.5	0.5–3.4
Compound S ng/mL	3.8	<8
Active renin μ UI/mL	25	7–76
Aldosterone pg/mL	62.9	40–310
Calcium mg/dL	9.5	8.8–10.6
Phosphate mg/dL	4.6	2.5–4.5
Magnesium mg/dL	2.1	1.9–2.5

25-OHD, 25-hydroxyvitamin D; ACTH, adrenocorticotrophic hormone; CEA, carcinoembryonic antigen; DHEA, dehydroepiandrosterone; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

Figure 2 Metaiodobenzylguanidine-I123 scintigraphy: cervical, thoracic and abdominal scans.

and tolerability, having accomplished this therapy until the first surgical intervention.

The patient underwent bilateral laparoscopic adrenalectomy, without any associated complications. Histopathological examination of the surgical specimens revealed bilateral benign pheochromocytomas, the right with 11.0 cm and the left with 8.5 cm of larger diameters. Immunohistochemical study revealed Ki67 of 2%, with additional positivity for chromogranin, synaptophysin and S100 (figure 3). After the surgical procedure, steroid replacement therapy (hydrocortisone and subsequently fludrocortisone) was introduced, with progressive dose titration. In the successive reevaluations after the postoperative period, the patient remained clinically stable and the analytical evaluation demonstrated significant reduction in the levels of serum and urinary metanephrines, as well as in VMA levels. However, she maintained with persistently high levels of calcitonin and carcinoembryonic antigen (CEA).

Approximately 2 months after bilateral laparoscopic adrenalectomy, the patient was submitted to total thyroidectomy with central lymph node dissection, also without postoperative complications. The histopathological study revealed a tumorous lesion in the left lobe, with 11 mm diameter, surrounded by a fine fibrous capsule, which was permeated at multiple points by the tumour, nonetheless without extrathyroid extension. Two pretracheal lymph nodes were also identified, both without neoplastic infiltration. The immunohistochemical evaluation demonstrated positivity for calcitonin as well as for TTF1, with no expression for thyroglobulin, compatible with medullary thyroid carcinoma—pathological tumour node metastasis (pTNM)—T1b; R0. AJCC: I (N0; M0) (figure 4). In the post-surgical evaluation, the patient persisted clinically stable under replacement therapy. We observed a progressive normalisation of calcitonin and CEA levels.

OUTCOME AND FOLLOW-UP

The patient remained clinically stable after the surgical procedures, without immediate associated complications and with no signs of adrenal insufficiency or hypothyroidism, remaining under steroid and levothyroxine replacement therapy (hydrocortisone, fludrocortisone and levothyroxine sodium), with progressive dose titration, as described.

During the follow-up examinations, the patient remained asymptomatic, with regular blood pressure and cardiac frequency. One year later, imaging exams—thyroid ultrasound plus abdominal CT—and biochemical tests—plasmatic and urinary metanephrines, calcitonin, CEA, PTH and calcium levels—were consistent with disease-free status for both pheochromocytomas and for MTC (table 2).

Figure 3 Histopathological and immunohistochemical evaluation confirming bilateral pheochromocytomas with benign behaviour. Positive staining of chromogranin A (A) and synaptophysin (B) and low Ki67 activity of 2% (C).

DISCUSSION

Pheochromocytomas are rare tumours, originated from the adrenal medulla and sympathoadrenal neuroendocrine system. Bilateral pheochromocytomas are more frequent in the presence of hereditary conditions such as MEN, VHL or NF1 and the possibility of the referred syndromes should always be sought with genetic evaluation, as previously described.

In respect to MEN2-associated pheochromocytomas, they are characterised by a more frequent secretion of epinephrine, bilateral adrenal involvement and reduced probability of malignancy.⁵ In addition, it is also known that the mutation in the codon 634 is related to the occurrence of bilateral adrenal lesions,⁷ as in the reported case.

Concerning the associated clinic presentation, patients with pheochromocytomas usually have a variety of symptoms related to the adrenergic overstimulation. Consequently, persistent or paroxysmal hypertension, palpitations, diaphoresis and headaches take part in the clinical spectrum of the disease, suggesting the diagnosis of pheochromocytomas with a specificity of 94% and a sensitivity of 91%.⁸ However, although the patient had been reporting the referred symptoms during a period of almost 2 years, the diagnosis was delayed, probably due to its paroxysmal characteristics.

The treatment with α 1-adrenergic receptor and β -adrenergic receptor blockage are both recommended in the preoperative period, during 7 to 14 days, to allow adequate normalisation of blood pressure and control the heart rate, respectively.¹ Some retrospective studies showed the association between α 1-selective adrenergic receptor blockage and inferior presurgical diastolic pressure, as well as lower intraoperative heart rate and improved postoperative haemodynamic recovery.⁹ On the other hand, there are also reports that did not show differences among selective and non-selective agents.¹⁰ In the described case, the patient received non-selective α -adrenergic blockade with phenoxybenzamine and β -adrenergic blockade with propranolol, during

14 days prior to surgery, presenting adequate tolerability and response, which may have contributed to decrease intraoperative and postoperative haemodynamic risks and complications.

Although laparoscopic adrenalectomy is recognised as a preferable surgical approach for pheochromocytoma, the practice of bilateral laparoscopic adrenalectomy is limited. However, open bilateral adrenalectomy is associated with an elevated rate of surgical complications, including intraoperative and postoperative bleeding (22%), pancreatic fistula, incisional hernia (10%) and wound healing impairment (13.5%), as well as other general complications.¹¹

The use of laparoscopy, particularly in the case of large tumours, has also been under debate due to the concerning of pneumoperitoneum, tumour manipulation and prolonged surgery duration, all of which could potentially increase catecholamine release.^{12–15} However, studies comparing open with laparoscopic surgery confirm the safety of the laparoscopic method, irrespective of tumour size.¹⁶

Rao and colleagues reported the results of a retrospective study about the outcomes of laparoscopic adrenalectomy for pheochromocytomas in patients with tumours smaller or greater than 4 cm.¹⁷ Operative times, blood loss and complications were comparable in the two groups, although the mean tumour size was more than two times greater in the group with the larger tumours. These findings are similar to those previously reported and support the belief that size alone may not be an optimal criteria in the selection of the surgical approach.^{12–18} Accordingly, bilateral laparoscopic adrenalectomy for larger tumours seems to be associated with no increase in adverse outcomes and may be considered as an adequate approach for these patients.

The clinical outcomes of 21 patients with Cushing and subclinical Cushing syndrome, undergoing adrenalectomy through transperitoneal lateral laparoscopic approach were retrospectively analysed by Conzo and colleagues. They reported that this technique may be considered as a safe and effective procedure,

Figure 4 Histopathological and immunohistochemical evaluation confirming medullary carcinoma of the thyroid; pretracheal lymph nodes without neoplastic infiltration-pTNM–T1bN0M0, R0; American Joint Committee on Cancer (AJCC): I. The H&E staining (A) shows tumour tissue composed of voluminous and polyhedral cells, with moderately pleomorphic nucleus. Positive staining of calcitonin (B) and thyroid transcription factor 1 (C).

Table 2 Laboratory assays during follow-up (one year after the diagnosis)

Analyte	Result	Reference value
ACTH pg/mL	8.1	9–52
Cortisol µg/dL	17	5–25
TSH µUI/mL	1.8	0.4–4.0
T4L ng/dL	1.5	0.8–1.9
PTH pg/mL	34	9–72
Calcium mg/dL	9.5	8.8–10.6
Calcitonin pg/mL	<2.0	<10
CEA ng/mL	0.5	<5.4
Plasma-free metanephrine pg/mL	17.9	<60
Plasma normetanephrine pg/mL	91.4	<120
Urinary metanephrines µg/24 hours	23.4	25–312
Active renin µUI/mL	7.1	7–76
Aldosterone pg/mL	17.0	40–310

ACTH, adrenocorticotrophic hormone; CEA, carcinoembryonic antigen; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

even for large adrenal lesions, with a morbidity level comparable to that described for other adrenal diseases. However, the authors highlight that the use of an additional port may be very useful, especially in case of complications. Moreover, a previous laparotomic surgery should not be considered as an obstacle for the described approach, being the tumour size proportional to the surgical skill required.¹⁹

More recently, Conzo and colleagues analysed through a systematic research the value of laparoscopic transperitoneal adrenalectomy (LTA), having compared this technique with posterior retroperitoneoscopic adrenalectomy (PRA). According to the authors, there has been a large reinforcement of both approaches as minimally invasive techniques in the last years; however, it is still debated which one is preferable. They stated that LTA may be considered as an effective and safe procedure even for pheochromocytomas with more than 6 cm in diameter, although patients with larger lesions usually have higher conversion rates and more hypertensive crises. The obtained outcomes of the two compared techniques were similar; however, thanks to the avoidance of pneumoperitoneum and the direct approach to the gland, PRA was associated with shorter operative time, less postoperative pain score and meaningfully shorter hospitalisation, with an equitable morbidity rate. Despite the described benefits, PRA may demand some difficulties especially with tumours larger than 8 cm in diameter, considering the smaller working space and implying substantial technical experience due to the change to a reverse angle approach.²⁰ Accordingly, additional studies are needed to compare these two approaches and define which one should be settled as superior.

Despite the previous reported studies, the suitability of laparoscopic approach for malignant adrenal tumours is still controversial. Considering that there are no infallible preoperative diagnostic tests to confirm the diagnosis of primary malignant adrenal tumour or local invasion, it is usually difficult to determine whether the laparoscopic approach can attain a curative resection. Additionally, there have been concerns about local recurrences and port-site metastasis after potentially curative resections.²¹

Recently, Sautter and colleagues presented a systematic review about the use of laparoscopic adrenalectomy for large malignant tumours. The referred study demonstrated a recurrence rate of 12.9% with laparoscopic adrenalectomy, compared with 36% of recurrence with open surgery.²² The report of a lower recurrence rate with the laparoscopic approach seems to be promising,

Learning points

- For all cases of pheochromocytomas, but particularly in the presence of bilateral lesions and presentation at young age, a genetic background should be sought.
- The α -adrenergic blockade is crucial in the preoperative management of hormonally functional pheochromocytomas and contributes to prevent cardiovascular complications.
- Laparoscopic simultaneous bilateral adrenalectomy can be a safe and feasible approach for pheochromocytomas in type 2 multiple endocrine neoplasia (MEN2) syndrome.
- In MEN2 syndrome, pheochromocytomas are usually benign.
- Due to the high risk of recurrence, patients with bilateral adrenal lesions should maintain long-term follow-up, even if presenting no evidence of disease.

nevertheless, it is relevant to recognise the possibility of a selection bias, considering that larger and more aggressive tumours were more probably treated with open adrenalectomy and the relatively short follow-up of the several studies.

Considering our case, it highlights the safety, feasibility and early patient recovery after simultaneous bilateral adrenalectomy. Thus, in the future, minimally invasive simultaneous bilateral adrenalectomy may be the preferable surgery for patients with MEN2, even in the presence of large lesions.

Finally, taking into consideration that the probability of recurrence is high, lifelong follow-up is recommended for these patients. In the case of genetic syndromes, this will not only promote the early detection of locally recurrent or metastatic disease, but also the early diagnosis of other components of the syndrome.

Contributors DM contributed to the diagnosis, management of the patient and manuscript writing; DR contributed significantly to managing the patient; MM contributed with the genetic evaluation of the patient and relatives and is responsible for the follow-up in the setting of medullary thyroid carcinoma; FC contributed to the manuscript editing.

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REFERENCES

- 1 Lenders JW, Duh QY, Eisenhofer G, *et al*. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915–42.
- 2 Lenders JW, Eisenhofer G, Mannelli M, *et al*. Pheochromocytoma. *Lancet* 2005;366:665–75.
- 3 Gimenez-Roqueplo AP, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. *Horm Metab Res* 2012;44:328–33.
- 4 Eng C. The *RET* Proto-Oncogene in Multiple Endocrine Neoplasia Type 2 and Hirschsprung's Disease. *N Engl J Med Overseas Ed* 1996;335:943–51.
- 5 Dralle H, Gimm O, Simon D, *et al*. Prophylactic thyroidectomy in 75 children and adolescents with hereditary medullary thyroid carcinoma: German and Austrian experience. *World J Surg* 1998;22:744–51.
- 6 Shen WT, Grogan R, Vriens M, *et al*. One hundred two patients with pheochromocytoma treated at a single institution since the introduction of laparoscopic adrenalectomy. *Arch Surg* 2010;145:893–7.
- 7 Tsang VH, Tacon LJ, Learoyd DL, *et al*. Pheochromocytomas in multiple endocrine neoplasia type 2. *Recent Results Cancer Res* 2015;204:157–78.
- 8 Machens A, Brauckhoff M, Holzhausen HJ, *et al*. Codon-specific development of pheochromocytoma in multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab* 2005;90:3999–4003.
- 9 Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 2002;26:1037–42.

- 10 Kocak S, Aydintug S, Canakci N. Alpha blockade in preoperative preparation of patients with pheochromocytomas. *Int Surg* 2002;87:191–4.
- 11 Yadav K, Bakshi G, Prakash G, *et al.* Simultaneous bilateral laparoscopic adrenalectomy for pheochromocytoma in multiple endocrine neoplasia (MEN) syndrome: case report with review literature. *Int J Surg Case Rep* 2014;5:487–90.
- 12 Carter YM, Mazeh H, Sippel RS, *et al.* Safety and feasibility of laparoscopic resection for large (≥ 6 CM) pheochromocytomas without suspected malignancy. *Endocr Pract* 2012;18:720–6.
- 13 Conzo G, Pasquali D, Della Pietra C, *et al.* Laparoscopic adrenal surgery: ten-year experience in a single institution. *BMC Surg* 2013;13(Suppl 2):S5.
- 14 Joris JL, Hamoir EE, Hartstein GM, *et al.* Hemodynamic changes and catecholamine release during laparoscopic adrenalectomy for pheochromocytoma. *Anesth Analg* 1999;88:16–21.
- 15 Kinney MA, Warner ME, vanHeerden JA, *et al.* Perioperative risks and outcomes of pheochromocytoma and paraganglioma resection. *Anesth Analg* 2000;91:1118–23.
- 16 Lodin M, Privitera A, Giannone G. Laparoscopic adrenalectomy (LA): keys to success: correct surgical indications, adequate preoperative preparation, surgical team experience. *Surg Laparosc Endosc Percutan Tech* 2007;17:392–5.
- 17 Rao N, Ramachandran R, Tandon N, *et al.* Laparoscopic adrenalectomy for pheochromocytoma—does size matter? A single surgeon comparative study. *Transl Androl Urol* 2016;5:780–3.
- 18 Toniato A, Boschin IM, Opocher G, *et al.* Is the laparoscopic adrenalectomy for pheochromocytoma the best treatment? *Surgery* 2007;141:723–7.
- 19 Conzo G, Pasquali D, Gambardella C, *et al.* Long-term outcomes of laparoscopic adrenalectomy for Cushing disease. *Int J Surg* 2014;12 Suppl 1:S107–S111.
- 20 Conzo G, Tartaglia E, Gambardella C, *et al.* Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic versus retroperitoneoscopic adrenalectomy and assessment of risk factors for complications. *Int J Surg* 2016;28(Suppl 1):S118–S123.
- 21 Zografos GN, Vasiliadis G, Farfaras AN, *et al.* Laparoscopic surgery for malignant adrenal tumors. *JSL* 2009;13:196–202.
- 22 Sautter AE, Cunningham SC, Kowdley GC. Laparoscopic adrenalectomy for adrenal cancer—a systematic review. *Am Surg* 2016;82:420–6.

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