Endocrinology, Diabetes & Metabolism CASE REPORTS

V de Miguel and others | Pheochromocytoma kidney transplantation

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Bilateral pheochromocytoma after kidney transplantation in neurofibromatosis type 1

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Summary

We present the case of a 25-year-old male with a history of neurofibromatosis type 1 and bilateral pheochromocytoma 4 years after kidney transplantation that was successfully treated with simultaneous bilateral posterior retroperitoneoscopic adrenalectomy.

Learning points:

- Hypertensive patients with NF1 should always be screened for pheochromocytoma.
- Pheochromocytoma is rarely associated with transplantation, but it must be ruled out in patients with genetic susceptibility.
- Posterior retroperitoneoscopic adrenalectomy (PRA) allows more direct access to the adrenal glands, especially in patients with previous abdominal surgeries.

Background

The prevalence of hypertension is very high in kidney transplant recipients and secondary causes should be excluded.

Neurofibrormatosis type 1 (NF1) is a common genetic condition with a prevalence of 1/3000. Pheochromocytomas (PHEOs) occur in about 0.1–5.7% of patients with *NF1* mutations (1).

We describe the case of a NF1 patient with bilateral pheochromocytoma (PHEO) diagnosed after kidney transplantation who was successfully treated with simultaneous bilateral PRA.

Case presentation

A 25-year-old man with a history of NF1 and end-stage disease due to congenital renal dysplasia underwent a second kidney transplantation 7 years ago. He was on immunosuppressive therapy with methylprednisolone, mycophenolate and tacrolimus.

Four years after transplantation, the patient presented sustained hypertension. His blood pressure (BP) was around 200/100 mmHg despite maximum doses of five antihypertensive drugs including diuretics. He reported episodes of sweating, headaches and palpitations.

He was admitted to our hospital for resistant hypertension and renal failure. Clinical examination revealed hypertension (BP: 210/110 mmHg), tachycardia (110 BPM), café-au-lait spots, skin neurofibromas and genu varum. Allograft nephropathy and renovascular disease were excluded.

BP was controlled with doxazosin, nebivolol and amlodipine.

Investigation

Computed tomography (CT) scans showed enlargement of the adrenal glands (Fig. 1A, B and C: Abdomen CT

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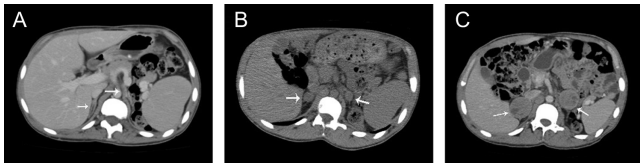

Figure 1
Abdomen CT scans follow-up. (A) Absence of native kidneys and normal adrenal glands (2010). (B) Abdomen CT scan showed enlargement of the adrenal glands 18 mm right and 16 mm left (2014). (C) Abdomen CT scan showed enlargement of the adrenal glands 43 mm right and 45 mm left (2016). Arrows indicate adrenal gland.

scans follow-up). The 24-h urinary metanephrines were highly elevated (Table 1).

Treatment

The patient underwent a successful bilateral (PRA) with two separate surgical teams that simultaneously performed the resection of the right and left tumor with no need to reposition the patient who remained in ventral decubitus. The operating time was 171 min. During surgery, there was a rise in BP that was controlled with intravenous phentolamine (total dose 31 mg) and labetalol. Pathology report confirmed PHEO diagnosis (Fig. 2A and B).

He is on prednisone and fludrocortisone therapy.

Outcome and follow-up

Two years after surgery, he is normotensive with no antihypertensive treatment. Renal function and urinary metanephrines are within the normal range.

Discussion

Pheochromocytoma in NF1

Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla that predispose to cardiovascular morbidity and mortality (2).

The incidence of PHEO in NF1 patients is relatively low compared to other hereditary syndromes. Most NF1-related-PHEO's are unilateral (84%), 10% are bilateral and a small percentage (6%) are extra adrenal or paragangliomas

Table 1 24-h urinary metanephrines (urinary volume 10 L).

Biochemistry	Result
Creatinine (0.7 a 1.1 mg/dL)	1.6 mg/dL
Urinary total metanephrines (150-1200 µg/24 h)	20.055 µg/24 h
Urinary metanephrines (50–400 µg/24 h)	5380 µg/24 h
Urinary normetanephrines (100–800 µg/24 h)	14675 µg/24 h

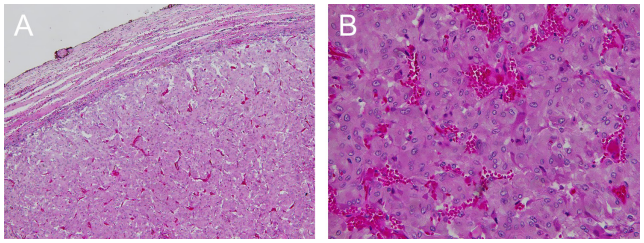

Figure 2
Microscopy. (A and B) Tumor proliferation constituted by fused cells in nests.

(PGL) (1, 2). Mayo Clinic reported in a cohort study from 1959 to 2015 that the prevalence of PHEO/PGL in patients with NF1 was 2.9% and the median age at the time of diagnosis was 41 years. Bilateral PHEO was identified in 17% of patients and metastatic or recurrent disease occurred in 7.3%. Mayo Clinic recommends biochemical test detection for PHEO/PGL every 3 years starting from 10 to 14 years, prior to elective surgical procedure and conception, and lifelong annual biochemical surveillance in patients with prior diagnosis of PHEO/PGL (3).

Renal transplantation and neoplasia

Neurofibromatosis (*NF1*) gene is a tumor suppressor gene that encodes for the protein neurofibromin. This protein downregulates the RAS signaling pathway. *RAS* is an important oncogene in human cancer and activates a number of signaling pathways such as MAP kinase and mTOR leading to proliferation and survival of *NF1*-deficient cells of nerve tumors and PHEO/PGL (1).

Cancer is more frequent after solid organ transplantation including the kidney. Younger patients appeared to be more affected and immunodeficiency-related malignancies are the more frequently seen (4). Only five patients with PHEO/PGL diagnosis after solid organ transplantation have been reported. None of them harbored NF1 or other hereditary cancer syndrome (5, 6, 7, 8, 9). Immunosuppression does not seem to play a significant role in these types of tumors. Compared to other NF1 reports, our patient was younger and had bilateral disease (1, 3).

Simultaneous PRA

Although laparoscopic adrenalectomy is the preferred therapy for pheochromocytoma, experience with simultaneous laparoscopic bilateral adrenalectomy is limited (10). The large work space and easiness to find anatomical landmarks made the transperitoneal approach the one used most often in our midst. Since the adrenal glands are two small organs located deep

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in the abdomen surrounded by retroperitoneal fat, therefore having a right exposure can be difficult. In this context, retroperitoneoscopic surgery is an interesting option that allows a more direct access to the adrenal gland, especially in cases such as our patient with significant history of abdominal surgeries and bilateral adrenal tumors. Not repositioning the patient, avoiding the abdominal cavity, addressing a simultaneous and synchronous adrenalectomy and offering a minimally invasive approach were perhaps the main advantages. Nevertheless, the PRA technique has certain drawbacks, such as instrument clashing and limitations of working in a small space.

It is very important to perform a strict intraoperative monitoring of BP, since anesthetic induction, the creation of the pneumoretroperitoneum and the manipulation of the tumor produce great release of catecholamines. In our patient, despite simultaneous resection of both tumors, adequate control of BP was maintained with high doses of intravenous phentolamine and labetalol.

Conclusion

In conclusion, patients with NF1 have risk of PHEO/PGL. The excess of catecholamines carries a significant morbidity and mortality risk if diagnosis is missed. Although these tumors are rare causes of hypertension after kidney transplantation, it is important to consider them especially in patients with predisposing genetic syndromes. A correct diagnosis is essential for definitive surgical management. Follow-up in our patient will include lifelong annual biochemical testing with 24-h urinary metanephrines for early detection of recurrent disease (3). This case highlights the safety, feasibility, early recovery and good outcome when performing a simultaneous bilateral adrenalectomy, as well as the importance of having a multidisciplinary approach that allows a successful treatment of this challenging disease.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written, informed consent has been obtained from the patient for the publication of this article.

Author contribution statement
Valeria de Miguel and Andrea Paissan: Endocrinologists of the patient. Patricio García Marchiñena and Alberto Jurado: Urologist-of the patient (Surgical team). José Alfie: Clinician of the patient. Mariana Isola: Pathologist. Patricia Fainstein Day: Endocrinologist (Chief) Collaborate with the discussion.

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