An Uncommon Presentation of Pheochromocytoma in Neurofibromatosis Type 1 and the Importance of Long-Term Follow-Up

Uma Apresentação Rara de Feocromocitoma na Neurofibromatose Tipo 1 e Importância do Seguimento a Longo Prazo

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ABSTRACT

Neurofibromatosis type 1 (NFT1) is a disease caused by mutations in the tumor suppressor gene NF1. It is associated with a higher incidence of chromaffin cell tumors which are usually adrenal, unilateral and benign. The presence of these tumors during pregnancy is extremely rare and frequently associated with fatal outcomes. We report the case of a female patient with NFT1, who presented with paroxysmal spells of headache, palpitations, dizziness and pre-cordial discomfort, starting immediately after the delivery of her third child. Diagnostic work-up came to reveal a bilateral pheochromocytoma and the patient underwent bilateral adrenalectomy. Over 12 years after the initial surgery, metastatic disease was diagnosed, and a reintervention was performed. This is a rare presentation of bilateral malignant pheochromocytoma in a patient with NFT1, with postpartum occurrence of the first symptoms. This text focuses the important details and challenges found at each stage of diagnosis and follow-up.

Keywords: Neurofibromatosis 1; Pheochromocytoma

INTECRODUCTION

Neurofibromatosis type 1 (NFT1) is an autosomal dominant disease that results from germline mutations in the tumor suppressor gene NF1.1

Pheochromocytoma is a rare tumor that originates in the chromaffin cells of the adrenal glands.2 Several syndromes have been associated with an increased frequency of pheochromocytoma/paragangliomas.3,4 Approximately 0.1% - 5.7% of NFT1 patients develop chromaffin cells tumors,5 which are mostly adrenal and unilateral (93%) with metastatic disease occurring only in 7.3%.6 The presence of pheochromocytomas during pregnancy is an extremely rare occurrence and, in most cases, the diagnosis is made in the context of hypertensive crisis with serious/fatal consequences.7

CASE REPORT

A 31-year-old, female patient with a clinical diagnosis of NFT1 presented with holocranial headaches, dizziness, palpitations and precordial discomfort, immediately after the delivery of her third child. The episode lasted for a few minutes and had spontaneous resolution.

Analogous episodes occurred during the following years as paroxysmal events, with no relation with exertion and reached a weekly periodicity. She started follow-up in an Internal Medicine clinic and a cardiac study was ordered with a 24-hours Holter registering elevated mean heart rate due to the presence of sudden periods of tachycardia. An abdominal computed tomography was requested, and nodular masses were seen in both adrenal glands with 5.4 x 8.9 cm on the right and 5.2 x 4.9 cm on the left, solid and with heterogenous postcontrast enhancement. Due to suspicion of pheochromocytoma, urine metanephrines and vanillylmandelic acid (VMA) measurements were requested.

At age 33, during another paroxysmal crisis, the patient presented in the Emergency Department and was admit-
ted in order to complete the study. The requested urine tests were already available, revealing urine metanephrines > 1500 μg/24 hours (reference range-RR < 1000) and VMA 38.5 mg/24 hours (RR 1-8). An 123I-metaiodobenzylguanidine (123I-MIBG) scintigram was requested, which showed masses in the topography of both adrenal glands, intensely fixating; with some authors currently suggesting systematic screening. Despite presurgical blockage, our patient experienced some periods of hemodynamic instability during the first surgical procedure. In fact, possibly due to its secretory profile, pheochromocytomas in patients with NFT1 have been associated with a more unstable hemodynamic course.

In the initial postoperative evaluation, there was normalization of the biochemical markers. She was kept under follow-up in an Internal Medicine, and later also in an Endocrinology clinic. Urinary and later fractioned plasmatic metanephrines and normetanephrine were performed yearly and were within the reference range during the first 13 years postsurgery. Cervico-toraco-abdominal computed tomography alternating with magnetic resonances were performed every 1-2 years and the results were unremarkable, except for the detection, seven years after surgery of residual left adrenal tissue. The possible coexistence of other endocrinopathies was also screened and no other significant abnormalities were found.

At 47 years of age, a thoracic magnetic resonance imaging revealed a right side 16x19 mm nodular lesion. Recent biochemical markers were unremarkable, a few months later, however, a de novo elevation of plasma metanephrine (185.7 ng/mL, RR < 60) and normetanephrine (247.9 ng/mL, RR < 120) was detected and confirmed in another sample. A fluoroDOPA-F18 positron emission tomography (FDOPA-F18 PET) scan documented a right broncho-hilar nodular lesion with intense F-DOPA uptake, suggesting a neuroendocrine tumor/pheochromocytoma lymph node metastasis (Fig. 2).

After a 15-day period of presurgical preparation, the broncho-hilar lesion was excised. The procedure was uneventful. The histologic examination revealed a well-defined lesion, partially covered by a thickened fibrous capsule, consisting of nests of cells with marked pleomorphism and evident nuclei, with occasional figures of mitosis. Neoplastic cells showed strong and diffuse expression of chromogranin, synaptophysin and SDHB. Ki67 was < 1%. Thus, a metastasis of pheochromocytoma was confirmed (Fig. 3).

In the first biochemical control post-surgery the patient displayed normal plasmatic metanephrines (20.5 pg/mL; RR < 120). The FDOPA-F18 PET performed seven months later did not suggest local or metastatic disease.

Currently, 24 months after surgical excision of the bronchial metastasis, the patient is clinically well, without biochemical abnormalities or imaging signs suggestive of neoplastic recurrence.

DISCUSSION

The diagnosis of pheochromocytoma/paragangliomas is challenging due to the frequently non-specific clinical presentation. These tumors entail a high risk of complications and limiting screening to symptomatic NFT1 patients may leave some cases undiagnosed, with some authors currently suggesting systematic screening. The hypertensive crisis that our patient experienced immediately after parturition was most likely the first overt manifestation of the tumor. This postpartum presentation occurred without overt prior symptoms and, more importantly, it did not have major consequences, which contrasts with most cases of undiagnosed chromaffin cell tumors during pregnancy described in the literature.

Our patient had an adrenal epinephrine and normetanephrine secreting tumor, as is common in NFT1; however, she presented bilateral malignant disease which is unusually seen in these patients. Surgical resection is the cornerstone of therapy and presurgical preparation with α-blockage is standard treatment to avoid intraoperative hypertensive crisis. Despite presurgical blockade, our patient experienced some periods of hemodynamic instability during the first surgical procedure. In fact, possibly due to its secretory profile, pheochromocytomas in patients with NFT1 have been associated with a more unstable hemodynamic course.

In the presented case, the first histological report of necrosis and vascular invasion depicted worrisome prognostic signs. The fact that a remainder of the left adrenal was identified might also have contributed to metastatic disease, however no signs of local recurrence were documented. Our patient developed metastatic disease over 12 years after the initial tumor resection and interestingly the asymptomatic presentation of the metastatic disease sharply contrasted with the florid clinical picture associated with the primary tumor. These aspects support current recommendations for lifelong clinical, biochemical and imagiological follow-up of pheochromocytomas/paragangliomas in the presence of genetic disease.

On an important note, the presence of syndromic disease is demanding for the patient, and exhaustion in maintaining follow-up may occur. Therefore, patient education and support is essential.
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AUTHORS CONTRIBUTION
IV: produced the initial report and performed the literature review.
VA: reviewed the histologic samples and provided the histological images.
CM, VA, IP: reviewed the initial report, contributed to its scientific accuracy and assisted in creating the final version. All the authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS
The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY
The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

PATIENT CONSENT
Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

CONFLICT OF INTEREST
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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REFERENCES

Figure 1 – (A) Left pheochromocytoma with prominent nuclear pleomorphism and high cellularity areas (100x); (B) Capsular invasion was documented on both sides (100x).

Figure 2 – FDOPA-F18 PET scan revealing a right broncho-hilar nodular formation with intense F-DOPA uptake suggestive of either a neuroendocrine tumor or a pheochromocytoma lymph node metastasis
Figure 3 – Pheochromocytoma metastasis on the right broncho-hilar region partly surrounded by a fibrous capsule (inferior right corner, 40x).