ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

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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Acta Med Port 2023 Jan;36(1):55-58 ▪ https://doi.org/10.20344/amp.16604

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

RESUMO

A neurofibromatose tipo 1 (NFT1) é uma doença causada por mutações no gene supressor de tumor *NF1*. Está associada a uma maior incidência de tumores de células cromafins que geralmente são adrenais, unilaterais e benignos. A presença destes tumores durante a gravidez é extremamente rara e com frequência associada a resultados fatais. Relatamos o caso de uma doente com NFT1, que apresentou crises paroxísticas de cefaleias, palpitações, tonturas e desconforto pré-cordial, com início imediatamente após o parto de seu terceiro filho. A investigação diagnóstica revelou feocromocitoma bilateral e a doente foi submetida a adrenalectomia bilateral. Mais de 12 anos após a cirurgia inicial, foi diagnosticada doença metastática e efetuada reintervenção. Esta é uma apresentação rara de feocromocitoma maligno bilateral numa doente com NFT1, com ocorrência pós-parto dos primeiros sintomas. Este texto foca detalhes e desafios importantes encontrados em cada fase do diagnóstico e acompanhamento.
Palavras-chave: Feocromocitoma; Neurofibromatose 1

INTRODUCTION

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 admitted 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 ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigram was requested, which showed masses in the topography of both adrenal glands, intensely fixating the radiopharmaceutical substance. The presence of

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Recebido/*Received*: 24/05/2021 - **Aceite/*Accepted*:** 03/03/2022 - **Publicado *Online*/*Published Online*:** 08/04/2022 - **Publicado/*Published*:** 02/01/2023

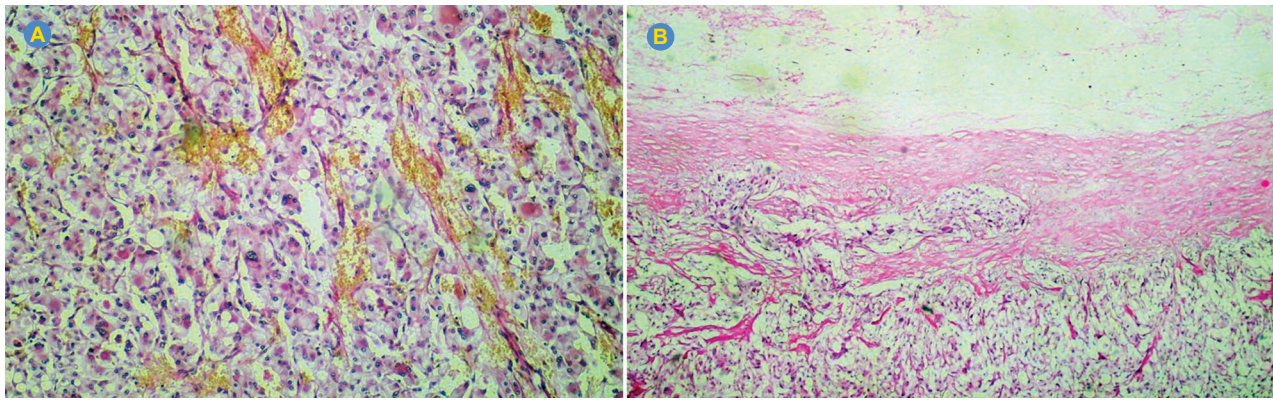

Figure 1 – (A) Left pheochromocytoma with prominent nuclear pleomorphism and high cellularity areas (100x); (B) Capsular invasion was documented on both sides (100x).

bilateral pheochromocytoma was assumed.

The patient was initiated on phenoxybenzamine and subsequently atenolol and bilateral adrenalectomy was performed a month later. During surgery, she had several hypertensive peaks that were controllable with nitroprusside, esmolol and fentolamin. In the immediate postoperative period, she was treated with stress doses of hydrocortisone and there were no significant complications. The histologic examination confirmed a bilateral pheochromocytoma with a pheochromocytoma of the adrenal gland scaled score (PASS) of four on the right and six on the left. Capsular compression, cortical gland distortion and vascular invasion were present on both sides; on the left there were areas of necrosis and cavitation, focal capsular invasion and venous tumoral embolism (Figs. 1A and 1B).

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

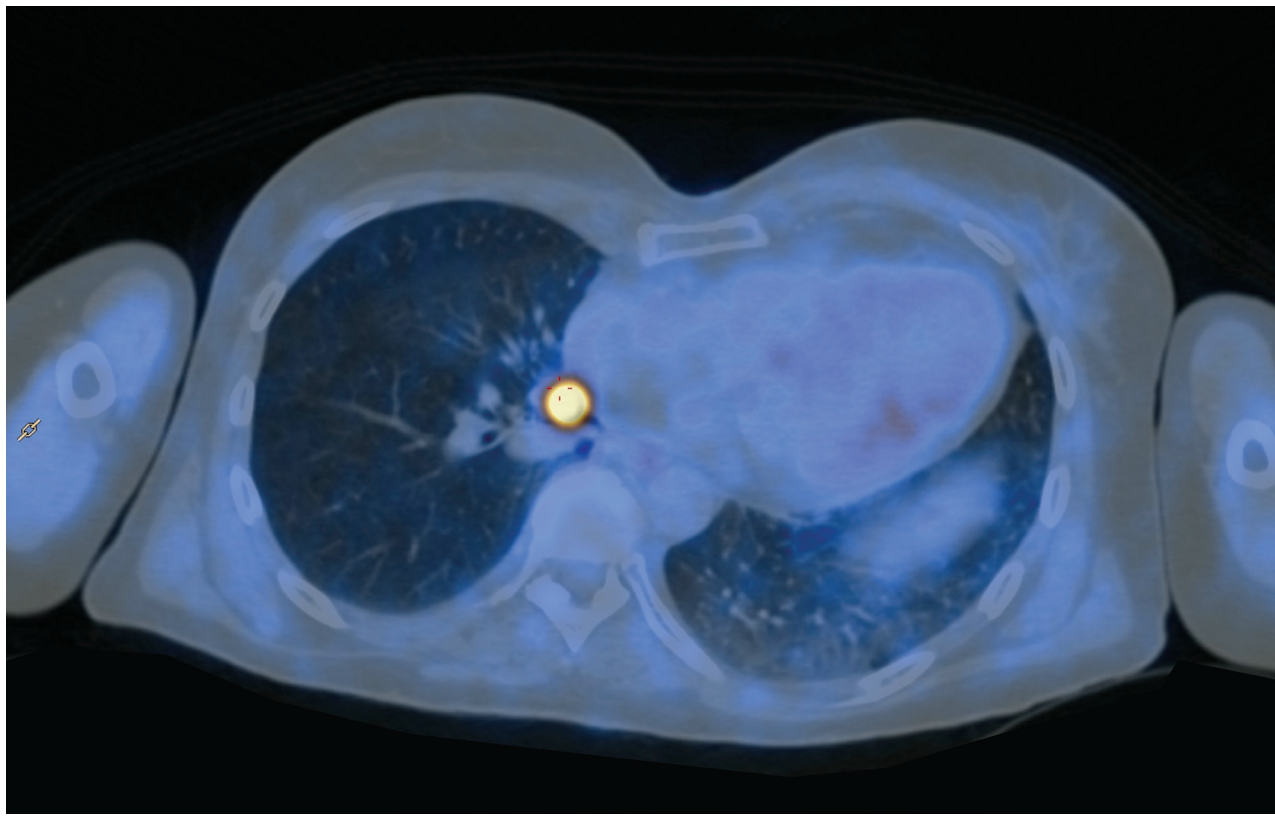

Figure 2 – FDOPA-F18 PET scan revealing a right broncho-hilar nodular formation with intense F-DOPA uptake suggestive of either a neuroendocrine tumor or a pheochromocytoma lymph node metastasis

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 significative 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 succinate dehydrogenase subunit B (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 < 60) and normetanephrines (116.3 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.[8,9] These tumors entail a high risk of complications and limiting screening to symptomatic NFT1 patients may leave some cases undiagnosed,[10–12] with some authors currently suggesting systematic screening.[6,10]

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.[7]

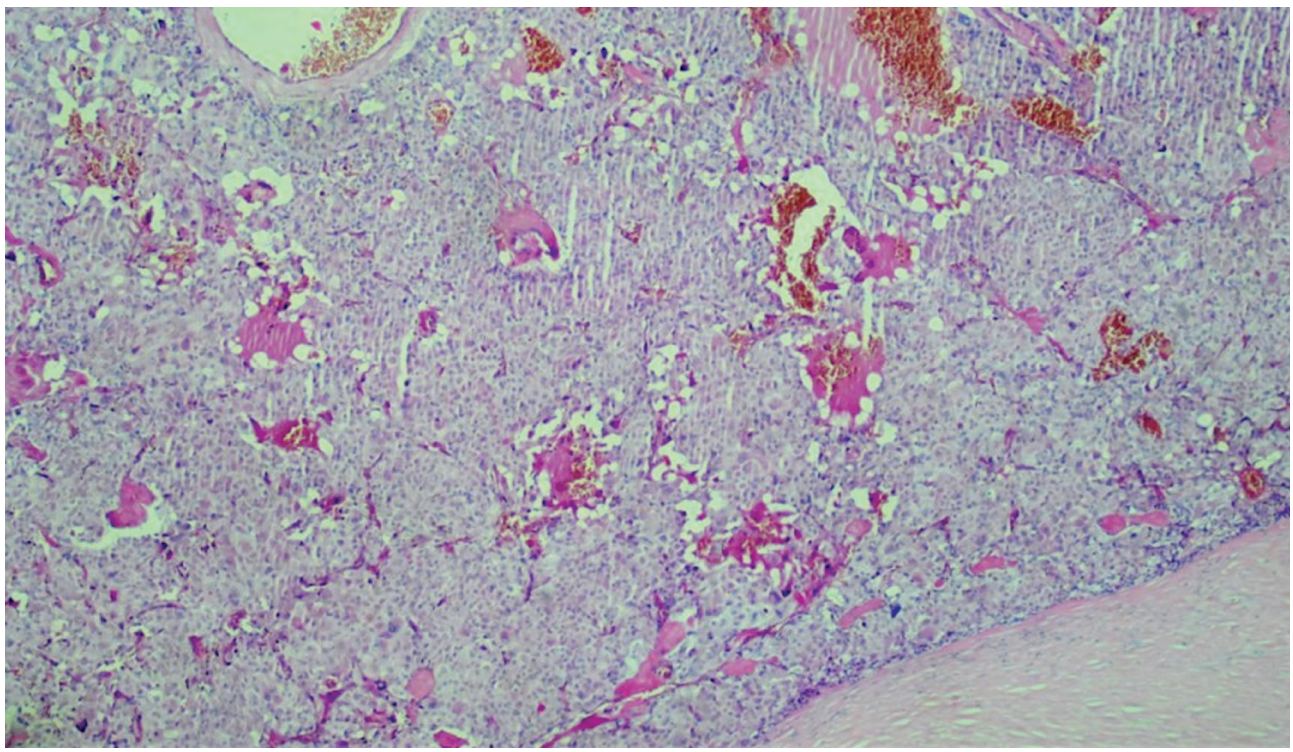

Figure 3 – Pheochromocytoma metastasis on the right broncho-hilar region partly surrounded by a fibrous capsule (inferior right corner, 40x)

Our patient had an adrenal epinephrine and normetanephrine secreting tumor, as is common in NFT1[5,13]; however, she presented bilateral malignant disease which is unusually seen in these patients.[6]

Surgical resection is the cornerstone of therapy and presurgical preparation with α-blockage is standard treatment to avoid intraoperative hypertensive crisis.[8] 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.[14]

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.[13]

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.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dírcea Rodrigues for her assistance in reviewing the manuscript.

AUTHOR CONTRIBUTIONS

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 reported, 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.

COMPETING INTERESTS

All authors report no competing interests.

FUNDING STATEMENT

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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