

Case Report

Tumoral Predisposition in type 1 Neurofibromatosis: A Case Report

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition that predisposes to a variety of primary neoplasias, having a wide presentation spectrum. Studies have suggested that the risk of developing benign and malignant tumors in NF1 patients could be approximately 2 to 5-fold higher than what is expected in the general population. We present the case of a 52-year-old caucasian man with NF1, recently diagnosed with a retroperitoneal Gastrointestinal Stromal Tumor (GIST). The patient had already been diagnosed with a Pheochromocytoma (PHEO) and a Papillary Thyroid Carcinoma (PTC) in the past. Here we discuss the rare concomitance of these three neoplasms in a NF1 patient, as well as the

clinical presentation and proposed oncological pathways linking NF1 to each of the neoplasms presented by the patient. To the best of our knowledge a similar set of tumors in a NF1 patient has never been described in literature.

Keywords: Neurofibromatosis type 1; Pheochromocytoma; Gastrointestinal stromal tumor; Papillary thyroid carcinoma; Case report

1. Introduction

Type 1 Neurofibromatosis (NF1) is an autosomal dominant disease, with an estimated global prevalence of 1 per 3000 individuals [1]. Although rare, NF1 is

the most common autosomal dominant disease affecting the nervous system and one the most frequent single gene disturbances in the general population [2]. NF1 occurs due to loss of function mutations in the NF1 gene, on chromosome 17q11.2, that codes neurofibromin-1 [3]. Neurofibromin-1's function is related to tumor suppression. The protein plays an important role in the regulation of cellular proliferation, differentiation, transformation and apoptosis, namely by downregulating RAS proto-oncogene pathway. Loss of function of this protein leads to an overactivation of this pathway and consequent uncontrolled cellular proliferation, culminating in an increased tumor predisposition. Literature describes a two to five-fold increased risk of developing a benign or malignant tumor, when compared to the general population [1]. NF1-related tumors most frequently develop in the skin as well as central and peripheral nervous systems [2]. Nevertheless, NF1 can predispose to primary tumors of other organ systems [1]. We present a clinical case of a NF1 patient with metachronous occurrence of 3 different tumors: Pheochromocytoma, Gastrointestinal Stromal Tumor and Papillary Thyroid Carcinoma. The occurrence of these three primary tumors in a single NF1 patient is rare, with no other cases reported in English language to this date.

2. Case Presentation

We report the case of a 52-year-old male patient, caucasian, independent in daily life activities. With a personal history of NF1, diagnosed in 2009, bilateral pheochromocytoma treated with bilateral adrenalectomy in 2009, PTC treated with right hemithyroidectomy in 2018, intracranial neurofibroma diagnosed in 2018 and dyslipidemia since 2019. He's usually medicated with hydrocortisone, fludrocortisone

and simvastatin, and presents a smoking history with a load of 45 pack-years, that ended in 2019. The patient was sent to an Endocrinology appointment in August/2018 because of a de novo increase in total urinary metanephrine (1413mcg/24h) and normetanephrine (1007mcg/24h) with normal plasma metanephrine and 3-methoxytyramine. He reported light to moderate headaches, for which he took acetaminophen with a good response, denying any other symptoms. At the physical examination, multiple subcutaneous neurofibromas, regions of hyperpigmented skin and multiple cafe-au-lait macules previously known in the context of NF1, were documented. No other alterations were found, namely in the blood pressure and heart rate. In the context of this history, and suspecting a relapse of PHEO, a 123I-MIBG Scintigraphy was carried out. This exam revealed an abdominal hypercaptation focus, adjacent to the right diaphragmatic crus (figure 1). To further investigate, a 68-Gallium-DOTANOC PET was requested, documenting a retroperitoneal nodule between the diaphragmatic crus and the inferior vena cava (IVC) (figure 2), compatible with malignant neoplastic tissue with high expression of somatostatin receptors. To clarify these findings, an MRI was requested. This exam confirmed the presence of two retroperitoneal nodules: one located posteriorly to the IVC, with an estimated dimension of 50 x 20 mm (figure 3); and the other anterior to the IVC and inferior to the right kidney, with 20 mm. Numerous augmented lymphatic nodes were identified between the left renal hilum and the pancreas tail, and adjacent to the mesenteric blood vessels. At this point a relapsed PHEO was considered as a probable diagnosis. The patient was seen in a Surgery appointment, and surgical resection was performed in September 2019. The histopathological exam,

however, showed a low grade (G1) GIST, with a fusocellular pattern, with 17mm of diameter, 0 mitosis/50 fields of 400x. No metastasis were found in the resected lymph nodes. The patient began to attend Gastroenterology consultations for follow-up. Given the grade of the tumor and the clinical stability,

without any gastroenterological signs or symptoms, a watchful waiting protocol was planned with periodical clinical appointments and twice-a-year laboratorial and radiological vigilance. Adjuvant therapy was not performed.

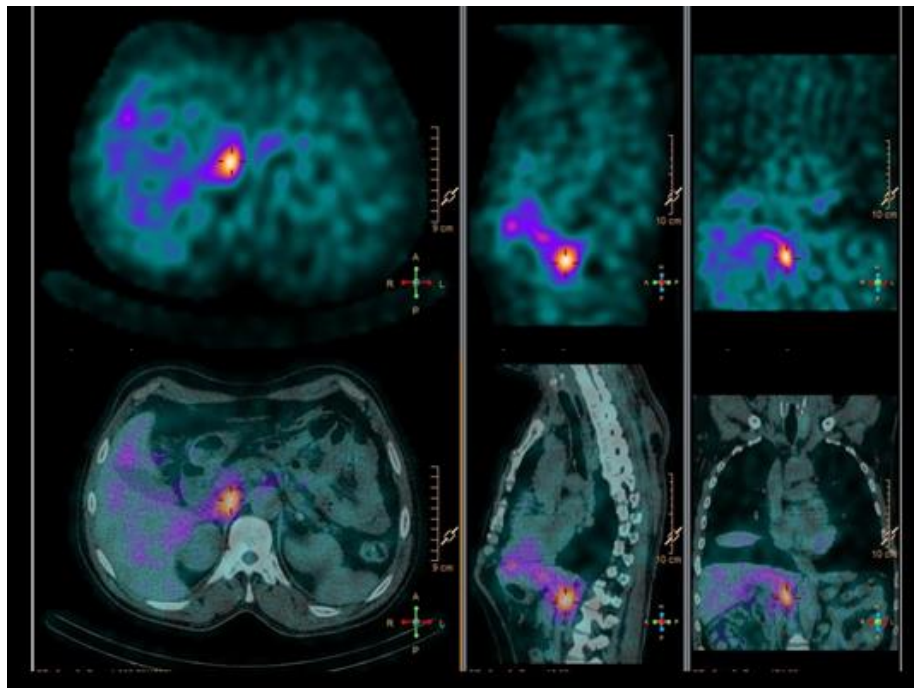


Figure 1: MIGB-scintigraphy showing a hypercaptating mass adjacent to the right diaphragmatic crux.

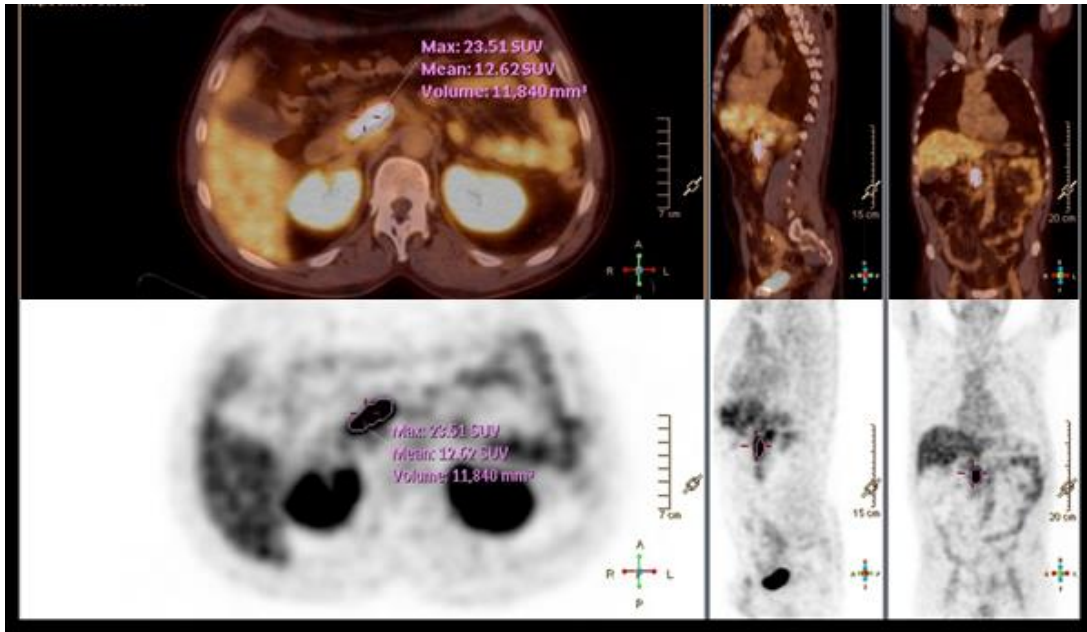


Figure 2: Gallium-68 DOTANOC PET showing a retroperitoneal mass between the right diaphragmatic crux and the inferior vena cava.



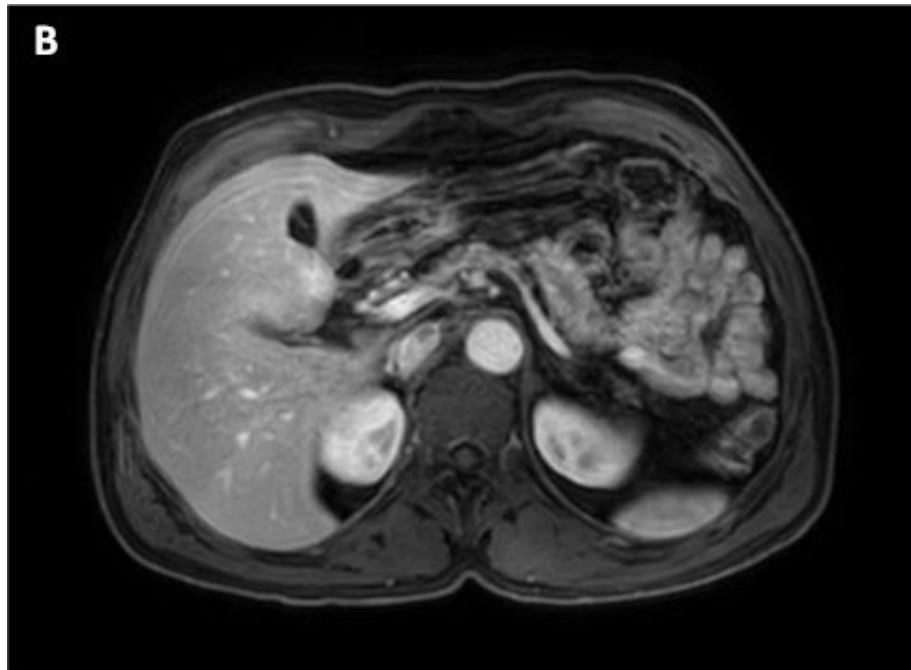


Figure 3: (A) MRI (T2 sequence, coronal cut) showing a retroperitoneal nodule measuring approximately 50mm of greater diameter. (B) MRI (mDixon sequence, axial cut) showing the same nodule posterior to the inferior vena cava.

3. Discussion

NF1 predisposes to multiple neoplasms, thus augmenting the probability of occurrence of successive primary tumours in the same individual. The association of NF1 with GIST and PHEO is well described, and an increased predisposition to some tumors of the thyroid gland is known as well.

3.1 Gastrointestinal Stromal Tumor (GIST)

GISTs occur in the general population at a rate of approximately 1.2 per 100,000 individuals per year [4] however in NF1 patients GISTs are reported in 5% to 25% of the patients [5]. These tumours originate from Cajal Interstitial Cells and, in sporadic forms, are most commonly associated with a gain of function mutation in c-kit proto-oncogene. In the case of NF1, the physiopathology is related with the loss of function of neurofibromin [6]. NF-1 related GISTs tend to develop

in the small intestine and its occurrence outside the gastrointestinal tract, as in the case we presented, is rare [5]. The clinical manifestations are variable and often unspecific or even nonexistent, especially in earlier stages of disease [7]. In NF1 patients, GISTs tend to be less aggressive than sporadic forms and have lower mitotic activity and smaller sizes at diagnosis, and consequently are associated with less symptoms and better prognosis [5]. In multiple cases the diagnosis is accidental in imaging studies [7]. When there is a clinical suspicion, endoscopy and/or imaging studies should be carried out, as well as a biopsy of the mass when feasible [5,8]. Treatment of NF1-related GISTs relies thoroughly on surgical resection. In sporadic forms with unresectable tumors, tyrosine kinase inhibitors, such as imatinib, are proven to increase overall survival, however, given the different

pathophysiology, NF1-associated GISTs show a primary resistance to these drugs. [4,5,8].

3.2 Pheochromocytoma (PHEO)

Although PHEOs occur in approximately 2-9.1 per 1,000,000 individuals in general population [9], it is estimated that 1-7% of NF1 patients develop these tumors [10]. PHEOs have their origin in chromaffin cells of the adrenal medulla therefore, the vast majority are metabolically active, secreting catecholamines (epinephrine, norepinephrine, and dopamine) as well as their inactive metabolites (metanephrine, normetanephrine and 3-methoxytyramine) [9,11]. Around 70% of PHEOs are hereditary, having been identified mutations in more than 30 genes associated its pathophysiology, some of these related to clinical syndromes. In NF1, the constitutional activation of RAS/MAPK and PI3/AKT pathways, caused by the loss of function of neurofibromin, is responsible for the hyperproliferation of chromaffin cells found in PHEO [9]. The symptoms of PHEO are variable, being the most commonly reported symptom hypertension [9]. However, according to literature, 10-15% of patients are asymptomatic [12]. In clinical suspicion, initial biochemical screening with plasma free metanephrines or urinary fractionated metanephrines measurement is recommended. If metanephrine levels are increased, imaging studies should be performed. CT scan is the preferred study for the initial evaluation. 123I-MIBG scintigraphy can be indicated when there is an increased risk for metastatic disease, namely in the presence of extra-adrenal or recurrent disease, such as in the case we present. 18F-FDG PET/CT is recommended in patients with known metastatic disease, and in this group of patients is even superior to 123I-MIBG scintigraphy in detection of metastasis. The treatment is mainly surgical, being laparoscopic

adrenalectomy recommended in most cases. In spite of this, open resection can be of use in some patients to ensure complete tumor resection, prevent tumor rupture and avoid local recurrence [13].

3.3 Papillary Thyroid Carcinoma (PTC)

PTCs are the most frequent malignant neoplasm of the thyroid gland, corresponding to 80-95% of thyroid malignancies [14]. These carcinomas are well differentiated and have their origin in thyroid follicular cells. Most PTCs occur in a sporadic fashion, having a multifactorial etiology and are typically associated with excellent prognosis and overall survival [15]. In spite of this, a minority of thyroid cancers are associated with familial syndromes and, in these cases, patients are typically younger and have more aggressive carcinomas, frequently presenting lymph node metastasis and extraglandular invasion at diagnosis [15].

4. Conclusion

NF1 associated PTCs are rare, with few reported cases and seldom information available in literature. Therefore, genetic and molecular mechanisms for this association are not yet fully understood [16,17]. RAS proto-oncogene mutations and consequent molecular pathways hyperactivation have been associated with the pathogenesis of sporadic PTC [14]. For this reason, some authors propose that the hyperactivation of RAS protein observed in NF1 may contribute to the pathogenesis of PTCs in these patients [16,17]. However, robust evidence that supports this hypothesis is still lacking. We present a patient with metachronous occurrence of three different primary tumors outside the nervous system. Although NF1 is associated with an increased incidence of GIST, PHEO and thyroid cancer, in our review of the current literature we found

no other publications reporting this set of tumors in the same patient. In addition to this a rare combination of tumors, this case as some other particular features such as the atypical clinical presentation of both GIST and PHEO. Furthermore, GIST, PHEO and PCT can have a very subtle clinical presentation in earlier stages, demanding a high clinical suspicion, to make an accurate definitive diagnosis and timely directed treatment. The case we present exemplifies the importance of a thorough follow-up of NF1 patients, to detect de novo primary tumors, as well as recurrence, in time for a potentially curable treatment.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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