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Case Report

Neurofibromatosis Type 1 – Association with Breast Cancer, Basal Cell Carcinoma of the Skin, and Low-Grade Peripheral Nerve Sheath Sarcoma: Case Report and Literature Review

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Neurofibromatosis type 1 · Nerve sheath neoplasms · Breast neoplasms

Abstract
Neurofibromatosis type 1 is a rare medical condition that raises the probability of having distinct types of malignant and benign neoplasms. Nevertheless, the association with breast cancer is rare, and metachronic neoplasia with a distinct histologic subtype is an association that has never been reported before. Here we describe a case of a primary breast tumor, with posterior development of basal cell carcinoma of the skin, and a low-grade peripheral nerve sheath sarcoma.

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Case Report

We report the case of a 55-year-old female patient with a past medical history of neurofibromatosis type 1 (NF1) (Fig. 1). Her son had NF1 and a high-grade sarcoma, a condition which resulted in death, and her daughter had NF1 with central nervous system glioma, without any other relevant background. The current 1-month illness of a mass in the right breast, associated with multiple axillary ipsilateral masses (6 adenopathies), with a tumor size of 3.5 × 3 × 2 cm, was biopsied finding an infiltrating ductal carcinoma, poorly differentiated grade III bloom Richardson, negative hormone receptors, Her2 positive (+++), and Ki67 80%. It was staged as IIB.

Due to the result of the pathology, it was decided to start with neoadjuvant chemotherapy, but the patient did not accept the therapy. Six months later, the patient went to follow-up due to tumor growth. A new biopsy was performed, and the result showed no changes in tumoral biology, and it was restaged as IIIC. For this reason, doxorubicin and cyclophosphamide were initiated as neoadjuvant therapy.

After the third cycle, the patient developed dyspnea, with deterioration in functional class, and chronic cough (20 days). The patient also mentioned headache of frontal location, which started early in the morning. For this reason, revaluation was indicated, and new images were taken. On computed tomography of the thorax, new pulmonary nodes were found (Fig. 2). In addition, on brain magnetic resonance imaging, an intraventricular solid nodular lesion adhered to the adjacent ependyma, adjacent to the splenium in the atrium of the left lateral ventricle was found, which, due to its features, suggested metastasis and less likely a subependymoma (Fig. 3). Also, the patient had an overgrowth of the tumoral mass located in the breast and more adenopathies.

After that, initiation of treatment with pertuzumab and trastuzumab was indicated. Nevertheless, the patient refused the treatment but accepted conformational radiation therapy over the lesion located on the central nervous system. For the tumoral overgrowth in the breast, the patient also agreed to a hygienic radical mastectomy with axillary emptying. The result of this new pathology showed no change in tumoral biology, and 14 lymph nodes were positive for metastasis.

The patient did not accept adjuvant chemotherapy, and during follow-up, two new lesions were documented, the first located on the lower eyelid with presence of basal cell carcinoma with a nodular pattern, and a right thigh lesion that was biopsied, finding a low-grade peripheral nerve sheath sarcoma.

Discussion

NF1 is a rare neuroectodermal disease that mainly affects the skin and nervous system. It is an autosomal dominant disorder that affects 1 in 3,000 individuals. This condition has high penetrance and a wide variability in expression [1]. In the skin, the predominant lesions are café-au-lait spots and multiple neurofibromas [2]. This condition is associated with various benign and malignant tumors including rhabdomyosarcoma, astrocytoma, and neurofibrosarcoma.

The involvement of breast cancer in patients with NF1 is a rare condition; however, these patients have an increased probability for developing breast cancer, varying between 3.5–10 fold, compared to the general population [3–5].

The diagnosis of breast cancer in these patients could be challenging due to the lesions presented on the skin of the chest, where biopsies are usually taken [6]. Also, the images usually taken to diagnose breast cancer are limited, as presented in the paper by Da Silva et al. [6], where the presence of neurofibromas in the breast hide the primary lesion.

Patients with NF1 who are younger than 50 years are at increased risk of developing breast cancer [4]. Other studies even found that women younger than 40 years old have a greater chance of acquiring this type of tumor [7]. The age-specific excess risk of breast cancer, comparing the NF1 cohort with the control cohort, was greater by 6.5-fold (95% confidence interval 2.6–13.5) in women aged 30–39 years. There was a 4.4 (2.5–7.0) times higher risk among women aged 40–49 [8].

It is unknown if the lack of neurofibromas is a primary or a secondary event in breast cancer tumorigenesis [9].

As for the tumor biology expressed by this population in the paper by Uusitalo et al. [7], 88.5% were ductal carcinomas and 7.7% lobular carcinomas. Luminal A was found in 15.4%, Luminal B in 34.6%, Her2 was amplified in 30.8% and triple negative in 19.2%. The basal-like phenotype was seen in 15.4%. Breast cancer was more often estrogen receptor negative and progestogen receptor negative [7]. Also, these patients had more extensive local compromise [1, 7, 10]. These findings were also present in our patient.

As for the mutational state, the percentage of BRCA1/2 mutations was 52%. With respect to prognosis, the overall survival was worse in the NF1 group: the 5-year survival was 68.1%. The patients with an NF1 mutation have a lower 5-year survival: only 77.1%, compared to those who do not have a documented NF1 mutation [7].

From the above, it can be inferred that these patients are at a high risk and could have a worse prognosis compared with the general population. Patients with NF1 are not treated as high-risk patients, and there are no special recommendations [3].

The gene of NF1 is located in the long arm of chromosome 17, a place where it is regulated by BRCA1. Its function is to regulate the conversion from active Ras-GTP to Ras-GDP. It is well known that Ras regulates growth, proliferation, differentiation, and apoptosis by being a tumor suppressor gene [3]. The most common mutation present in the NF1 gene is deletion [10].

Neurofibromin (encoded by the NF1 gene) functions as a negative regulator of the ras pathway, interacting with ras, converting active ras-GTP to Ras-GDP (inactive form) [11].

It has been proposed that haplodeficiency rather than total deficiency of neurofibromin is important for the development of neurofibromas in NF1. This model is proposed in patients with NF1 who develop gastrointestinal stromal tumors as part of the tumorigenesis pathway [12] and could be related to the appearance of breast cancer.

Deleterious NF1 pathogenic variants were identified in women. Frameshift mutations were found due to deletion, duplication, and complex rearrangement in 50% of the cases, nonsense mutation in 21%, in-frame splice mutations in 21%, and 1 case of missense mutation [13].

In some cases, the haplodeficiency of NF1 could complete the inexpression of neurofibromin by following the model of the double hit proposed by Knudson. The second hit theory in NF1 results in the loss function of the gene and could be important for tumor generation. Each tumor had a distinct genomic profile with mutually exclusive mutations in different genes.

Somatic NF1 mutation in the Schwann cells may trigger the formation of a neurofibroma [14]. NF1 aberrations can potentially lead to activation of the Ras, MAP kinase, and PI3K-mTOR pathways, resulting in proliferation of tumor cells [15].

Our case is similar to a case described by Schiff et al. [16], where the high incidence of developing a metastasis versus a glioma of the central nervous system is a difficult issue to

resolve. The patient had a metastatic mass of the primary colon cancer, but the challenge was related to attributing another mutation apart from NF1 to the development of a second neoplasm [16] that could not be identified in both cases.

Also, our patient developed a low-grade peripheral nerve sheath sarcoma, which is rare with an incidence of malignant sarcoma tumors of 2–10% in patients with NF1 [17]. Few cases of NF1 in association with other types of soft tissue sarcomas have been reported [18].

Conclusion

In patients with NF1, there must be a special follow-up screening for cancer in order to detect early breast neoplasm and other types of neoplasm, as seen in our patient who developed a primary breast tumor, another primary with a different histologic subtype, conditioning worst prognosis.

Statement of Ethics

Written Informed consent was obtained from the patient for the publication of this case report.

Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

M.I. Zapata Laguado, D.V. Lizarazo Hurtado, and C.E. Bonilla Gomez participated in the recollection of data and writing of the first draft. Z.M., A.J. participated in the search of the literature, drafted and translated the manuscript. All authors read and approved the final manuscript.

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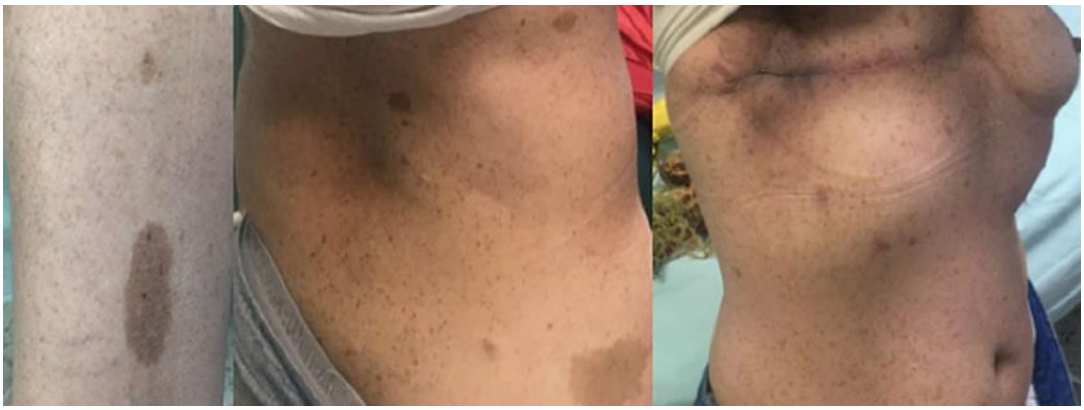

Fig. 1. Café au lait spots on the skin.

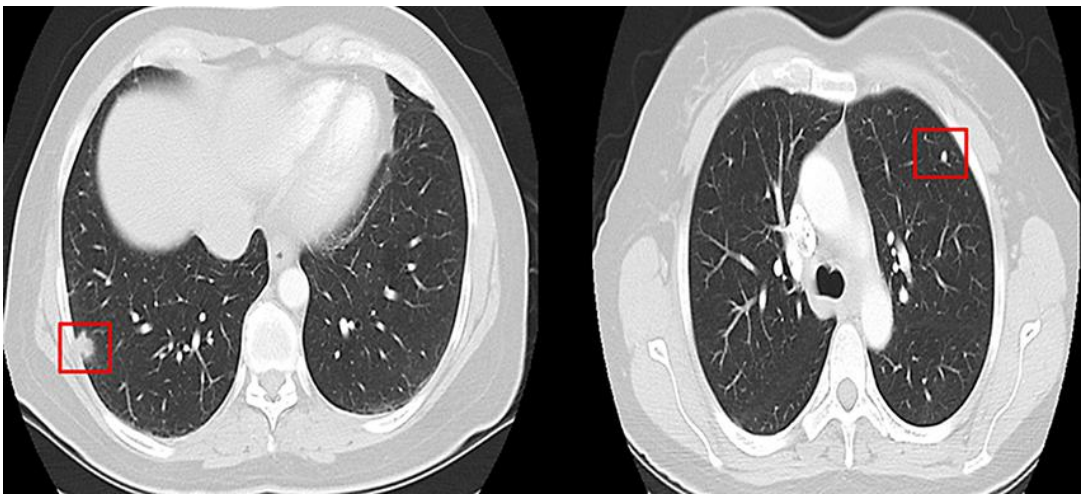

Fig. 2. Chest tomography exhibits pulmonary nodes, indicating progression of the disease.

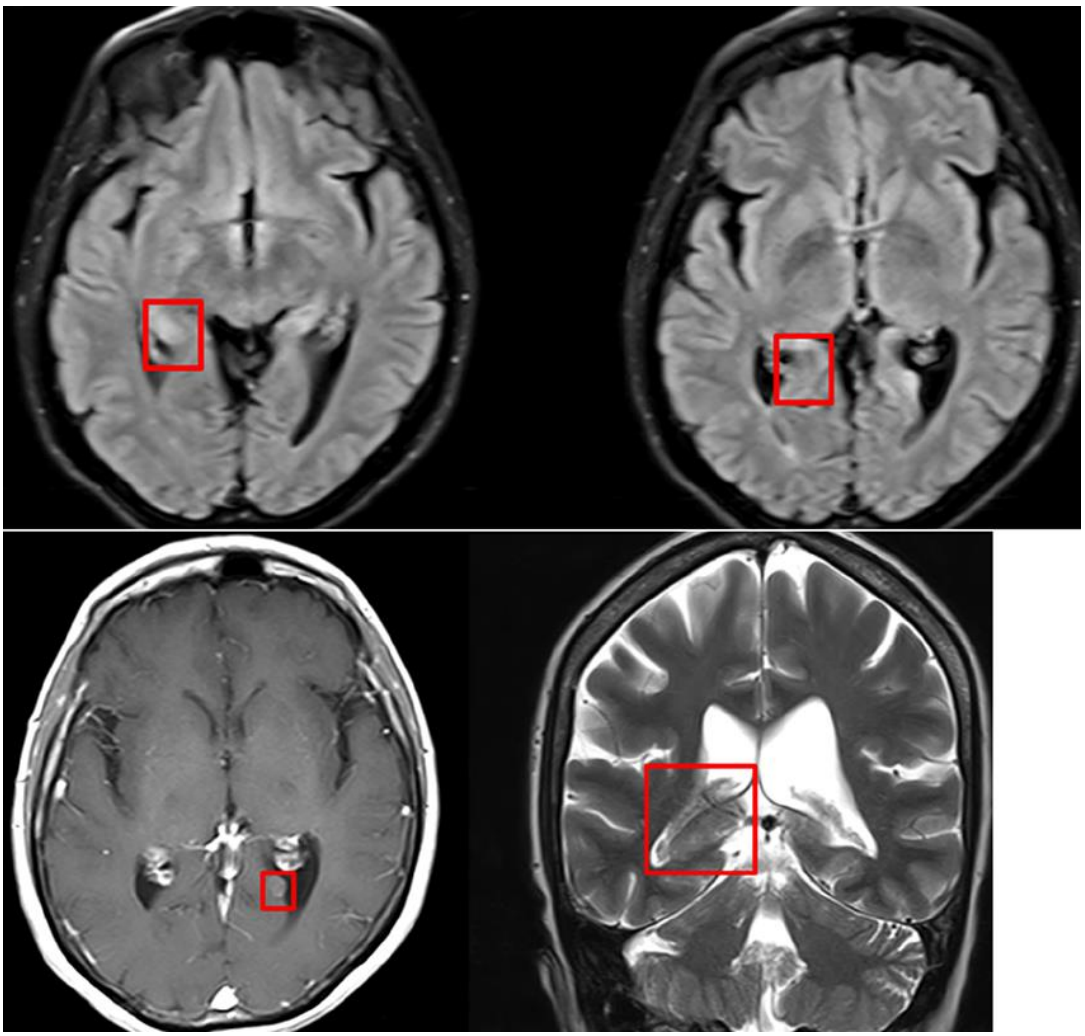

Fig. 3. Magnetic resonance of the brain exhibits an intraventricular solid nodular lesion adhered to the adjacent ependyma, adjacent to the splenium in the atrium of the left lateral ventricle that by its characteristics suggests metastasis and less probably a subependymoma.