Author's response to reviews

Title: Breast cancer and Neurofibromatosis 1: a diagnostic challenge in patients with high number of neurofibromas

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Version: 4 Date: 20 October 2014

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**Title**: Breast cancer and Neurofibromatosis 1: a diagnostic challenge in patients with high number of neurofibromas

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Abstract

**Background:** Neurofibromatosis 1 (NF1) is one of the most common genetic diseases in humans, presenting with multiple neurofibromas and increased risk of various benign and malignant tumors, including breast cancer.

**Case presentation:** In this paper we report a case of a woman with NF1 and the challenge to detect an advanced breast cancer because of numerous skin neurofibromas, which were responsible for an important delay in cancer diagnosis. Literature about the association of NF1 and breast cancer was reviewed and discussed.

**Conclusion:** Usual guidelines for breast cancer detection are not sufficient for the screening of NF1 carriers. More intensive clinical and radiological approach should be used if we are to achieve the same early detection rate as in non-NF1 women.

**Keywords**

Neurofibromatosis 1; Genetic diseases; Breast cancer; Neurofibroma; Secondary prevention

**Background**

Neurofibromatosis 1 (NF1) is one of the most common genetic diseases in humans, with a prevalence of one case in 3,000 births. It is caused by mutations in the NF1 gene, which is considered a tumor suppressor gene. NF1 presents a complete penetrance and a wide phenotypic variability. Multiple neurofibromas, café-au-lait spots, “freckling” in the inguinal and axillary regions and Lisch nodules develop in most affected individuals. Beyond the development of neurofibromas, which are benign peripheral nerve sheath tumors, NF1 patients present an increased risk for the development of other benign and malignant neoplasms, including gliomas, malignant peripheral nerve sheath tumors (MPNSTs), juvenile chronic myelomonocytic leukemia, rhabdomyosarcoma and pheochromocytoma. NF1 also represents a risk factor for the development of breast cancer.

The aim of this paper is to report a case of a 54-year old woman with NF1 and the challenge to detect an advanced breast cancer because of numerous skin neurofibromas and to review the literature about the association between NF1 and breast cancer.

**Case presentation**

A 54 year-old woman with the diagnosis of NF1 according to the National Institutes of Health criteria was referred to the Breast Service of the Hospital Universitário Antônio Pedro of Universidade Federal Fluminense by the Oral Diagnosis ambulatory from the same institution with the complaint of a “secretion from a mass in her left breast”. The patient reported she delayed to seek a physician because she though the mass was a manifestation of NF1.

On physical exam, the patient presented with thousands neurofibromas all over her body, including both breasts (Fig.1). Breast palpation reveled a large, tender mass occupying the whole breast, with approximately 10 cm in diameter. Identification of the nipple-areolar complex was difficult because of the extension of her neurofibromas. At consultation, a needle core-biopsy was performed, and histopathological analysis
revealed a ductal carcinoma in situ grade 1. Digital mammograms were performed, but they were very difficult to interpret due to the extension of the cutaneous disease. A large breast density associated with diffuse microcalcification was identified (Fig.2).

The clinical decision was to precede with a modified radical mastectomy and axillary clearance of levels I and II, due to the size of the mass. The surgical procedure was uneventful, with the skin incision contouring the neurofibromas. Of note, the skin flaps dissection showed some large vessels irrigating the skin, which calls for great care in the raising of the flaps. Level I and II of the axilla was dissected, where large but soft lymphonodes were noted. The healing process was normal, and the patient had a favorable evolution.

The histopathological analysis of the surgical specimen showed extensive high grade in situ carcinoma, comedo type, with 10 cm in diameter, located in all breast quadrants, associated with an invasive ductal carcinoma about 0,4cm in size. Histopathological diagnosis of neurofibromas was confirmed in the cutaneous lesions. Forty lymphonodes were isolated and presented only inflammatory reaction. Immunohistochemistry analyses were negative for estrogen receptor (ER), progesterone receptor (PR), pan-cytokeratin (pan-CK), S100, vimentin and epithelial membrane antigen (EMA). Ki67 were positive in 25-50% of the cells, and Her2-neu was positive 2+/3+. Fish essay was inconclusive due to exhaustion of the invasive component material in the paraffin block. There was a small invasion o the pectoralis fascia in the upper inner quadrant, not directly related to the tumor. Final pTNM staging was pT1N0M0.

She completed chemotherapy treatment (cyclophosphamide, methotrexate and fluorouracil, six cycles), and is currently on course of radiotherapy due to the size of the tumor.

**Discussion**

Although digital mammography is the gold standard for screening in early stage breast cancer, in this paper we show the challenge to interpret the images of a large breast carcinoma in a NF1 patient due to the high number of skin neurofibromas. Physical examination of this patient was also somehow impaired because of the amount of cutaneous lesions. The difficult in the detection of breast cancer in NF1 individuals with numerous skin neurofibromas was already described by other authors.(4,10,11) NF1 can dismiss or delay the identification of breast lesions not only because skin neurofibromas can obscure the signs of a malignant lesion, but also because patients and also physicians can mistakenly identify a breast mass as a manifestation of the primary disease.(9)

The first report of association of NF1 and breast cancer is from 1972.(12) After the first report, several other clinical cases of NF1 patients with breast cancer were presented in the literature.(4,9–11,13–17) Since breast cancer is a common tumor in female general population, the exact relationship between NF1 and breast cancer has been debated. The largest study on cancer prevalence in NF1 patients to this date is the one from Walker et al.(5), which showed that the overall risk of cancer was 2.7 times higher in a cohort of 448 NF1 patients than in the general population. The cumulative risk of a malignancy by age 50 years was 20%. Sharif et al.(6) identified 14 cases of breast cancer within a cohort of 304 NF1 patients older than 20 years, which represented a 4.9-fold risk of developing breast cancer to the age of 50. This represented a 8.4% cumulative risk of developing breast cancer; the risk in the general population was 2%.

The increased risk of breast cancer in NF1 patients appeared to be specific to women under 50 years of age.(6) Another population-based study found a 3.5-fold risk of breast
cancer in association with NF1 compared with the general population, with an apparent
tendency for patients to be diagnosed at a younger age.(18) Madanikia et al.(7), in a
cohort of 126 patients identified 4 cases of breast cancer, and found a trend for a nearly
3-fold increase in the risk of breast cancer in women with NF1 who were <50 years old
compared to age-matched unadjusted incidence rates.(7)

The data showing high prevalence and also suggesting a possible earlier onset of breast
cancer in NF1 individuals are particularly important due to the screening implications.(5)
Although breast cancer screening guidelines have been delineated for the general
population and for women with known genetic risk factors for breast cancer (i.e. BRCA1
and PTEN syndromes) in order to decrease mortality through early diagnosis, currently
there are no such guidelines for NF1 patients.(7)

A higher risk of breast cancer mortality rate of about 3.5 times in NF1 females comparing
to the general population was observed in a study with 1,186 NF1 individuals,
suggesting that there is not only increased risk for developing breast cancer, with a
earlier onset in women with NF1, but also a worse prognosis associated with the breast
cancer. As occurred in our patient, most of the cases of breast cancer in NF1 individuals
are diagnosed at an advanced stage with a T score greater than T2.(9,13) Therefore, the
worse diagnosis of breast cancer in NF1 may not be a characteristic of the disease itself,
but it may occur because patients are diagnosed at a late stage probably due to the
presence of skin neurofibromas, which hinders or confuses the identification of the
breast masses.(9) The most common histological type of breast cancer in NF1, as well
as in general population, is infiltrating ductal carcinoma, as observed in our case.(7)

The scientific data support a real association between breast cancer and NF1. With
regard to this, various authors have suggested different mechanisms supporting the
relationship between NF1 and breast cancer. One of the implicated events in
tumorigenesis of breast cancer is the overexpression of Ras protein, which occurs in up
to 60% of all cases and exerts several effects on cytoskeletal rearrangements, cell
survival and apoptosis through a number of mediators.(19) Neurofibromin, the protein
product of \textit{NF1} gene, which is located on chromosome 17q11.2, functions as a negative
regulator of the Ras pathway. It interacts with Ras and converts active Ras–GTP to its
inactive form, Ras–GDP. \textit{NF1} gene acts in accordance with the Knudson two-hit
hypothesis: in NF1-related tumors, biallelic inactivation of the \textit{NF1} gene results in
complete loss of functional neurofibromin activity.(13) Not only an upregulation of Ras,
but also an altered expression of neurofibromin, have been observed in breast cell lines,
suggesting overlapping etiologies.(13) However, it is not known whether the lack of
neurofibromin is a primary or a secondary event in breast cancer tumorigenesis.
Interestingly, about 28% of sporadic breast cancers in humans are missing at least one
copy of \textit{NF1} gene, either due to deletion or mutation.(15)

Mutations of the tumor suppressor genes \textit{BRCA1} and \textit{BRCA2} are known to be
associated with different patterns of hereditary breast/ovarian cancer syndrome.(13)
Since \textit{BRCA1}, like \textit{NF1} gene, is located on human chromosome 17q (17q12–q21), it has
been suggested that could have an interaction between these two genes. While it is
probable that some individuals reported in the literature carried mutations in both \textit{BRCA1}
and \textit{NF1} genes, there is a scarcity of studies which investigated the molecular evidence
of the involvement of germline mutations in these two genes in the same individuals.(13)
To the best of our knowledge, Campos et al.(13) were the only to report a family with
some members clinically affected by NF1 and breast cancer, being carriers of both
\textit{BRCA1} and \textit{NF1} mutations.(13) They concluded that the concurrence of NF1 and breast
cancer is probably due to the simultaneous existence of two cancer predisposing
conditions.
**Conclusion**

In conclusion, for early detection, it seems that the general guidelines used to screen women in the general population are not sufficient for this particular group of NF1 patients. Scientific data justify earlier screening programs designed specifically for this group, including annual physical examination by a breast specialist. The problems presented by interpreting the mammograms calls the attention of a need for more intensive radiological exams in patients with high number of neurofibromas, such as ultrasound and magnetic resonance imaging (MRI), which sensitivity is unlikely to be affected by the cutaneous lesions. It is important that patients and physicians are aware of the increased risk of breast cancer in the subset of NF1. It is clear that more robust studies are necessary to clarify the relationship of NF1 and breast cancer and also to trigger positive actions in order to allow earlier diagnosis and hopefully decrease breast cancer associated morbidity and mortality in women with NF1.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

AVS attended the patient; MP made the pathological diagnosis; AVS and KSGC contributed to the conception, design and preparation of the manuscript; FRR and VGSL revised the manuscript and gave important contributions to the histopathological interpretation. All authors read and approved the paper.

**Acknowledgements**

This research has not been supported by any grant or fund.
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