CASE REPORT

Breast Cancer in Neurofibromatosis Type 1: Screening, Diagnostic and Therapeutic Challenges – A Case Report

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ABSTRACT

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by an increased risk of various tumours, including breast cancer, particularly in women under 50. This case report discusses a 47-year-old woman with NF1 who was diagnosed with metastatic invasive ductal carcinoma of the breast. She initially presented with respiratory symptoms, and subsequent clinical evaluation revealed a left breast ulcer and underlying mass, which the patient had attributed to NF1-related cutaneous changes. Histopathological examination confirmed bilateral hormone receptor positive, HER2-negative invasive breast carcinoma with metastatic involvement. Management options, including systemic therapy, were discussed within a multidisciplinary team, and the patient elected to proceed with endocrine therapy using Tamoxifen. This case highlights the clinical complexity of breast cancer detection in individuals with NF1, where overlapping benign cutaneous manifestations may influence symptoms interpretation. It also highlights the importance if early and regular breast cancer screening, beginning at age 30, using appropriate imaging modalities such as mammography and contrast-enhanced breast MRI. Individualised screening strategies patient education remain essential to optimise outcomes in this high-risk population.

Keywords
neurofibromatosis type 1, breast cancer, screening, early detection

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that increases the risk of tumour formation. It is primarily marked by the growth of multiple neurofibromas along the peripheral nerves. The condition occurs in about 1 in 2,500 to 3,000 births.[1] While NF1 is primarily recognized for its dermatological and neurological manifestations, it also predisposes patients to various tumours, including breast cancer. Studies indicate that women with NF1 have a 3- to 5-fold higher risk of developing breast cancer, particularly those under the age of 50.[2] Diagnostic delays are common in NF1 patients due to overlapping skin lesions and atypical presentations that may obscure malignancies. Therefore, early detection through routine mammography, clinical breast examinations and patient education is essential for timely diagnosis and intervention.[3]

CASE PRESENTATION

A 47-year-old woman with a known history of neurofibromatosis type 1 (NF1), diagnosed during adolescence with generalised lesion, but not under regular follow-up, presented with respiratory symptoms and significant unintentional weight loss over five months. Further clinical assessment led to hospital admission,

where she was treated for acute pulmonary oedema related to a hypertensive emergency and subsequently followed up in a primary care setting.

Her symptoms persisted and comprehensive physical examination later revealed an ulcerated lesion in the lower outer quadrant of the left breast, associated with a firm underlying mass measuring approximately 3x3 cm (Figure 1). The patient had not previously reported this lesion, as it was initially perceived to be related to NF1-assocaited cutaneous changes. Additional history revealed that the lesion began as a pruritic area overlying a neurofibroma.

Breast imaging demonstrated a large irregular hypoechoic mass in the left breast at the 2:00–3:00 position, near the areola, measuring 2.3 x 4.2 x 5.8cm categorized as BIRADS 5. An additional irregular lesion was identified in the right breast at the 12 o'clock position, 2 cm from the nipple, measuring 0.7 x 1.0 x 0.7 cm, categorized as BIRADS 4A (Figure 2). Computed tomography of the thorax, abdomen and pelvis (CT TAP) revealed bilateral breast mass with metastases to the lung and bones.

Histopathological examination of biopsies from both breasts confirmed invasive breast carcinoma that was oestrogen receptor (ER)-positive, progesterone receptor (PR)-positive and HER2 negative. (Figure 3). The patient was managed through a multidisciplinary approach involving the breast and endocrine surgical team as well as the oncology team provided holistic management. Systemic treatment options, including palliative chemotherapy and endocrine therapy were discussed and the patient elected to proceed with endocrine therapy using Tamoxifen.

Figure 1: An irregular ulcer at the lower outer quadrant of the left breast, measuring 3x3cm with multiple cutaneous neurofibromas and café au lait spots.

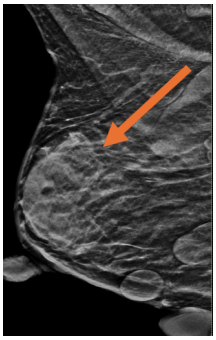

Figure 2: Mammogram of right breast shows large irregular hypoechoic mass seen at 2:00 -3:00 periareolar region, measuring 2.3x4.2x5.8cm (BIRADS 5)

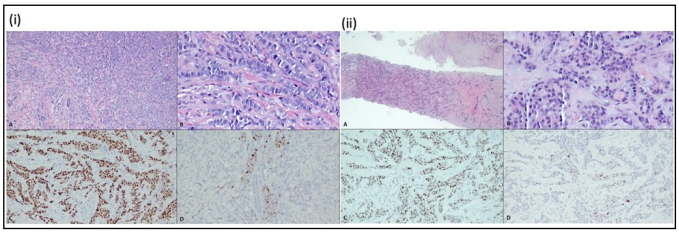

Figure 3(i and ii): Histological features of both right and left breast tumour biopsies are of same morphology. (A) The tumour is composed of malignant ductal cells arranged in cords and sheets (H&E, 10x). (B) The malignant cells show pleomorphic nuclei and inconspicuous nucleoli (H&E, 40x). The malignant cells are also positive for (C) Oestrogen receptor (IHC, 20x) and (D) Progesterone receptor (IHC, 20x).

DISCUSSION

NF1 is a hereditary illness marked by the formation of many benign tumours known as neurofibromas, as well as other symptoms such as café-au-lait spots and freckling. Approximately 50% of individuals impacted by NF1 exhibit a positive family history, whereas the other 50% are attributed to de novo mutations. Sporadic occurrences of NF1 are caused by spontaneous mutations in the NF1 gene, which can emerge in individuals with no family history of the condition.[4] In this case study, this patient has sporadic NF1, as no other family members have a similar skin condition.

People with NF1 have a heightened likelihood of developing cancerous tumours, including breast cancer, in comparison to those who do not have the condition. These malignancies can reduce the average life expectancy of people with NF1 by 10 to 15 years.[5] The NF1 gene is located on the long arm of chromosome 17, near the BRCA1 gene. Both are tumour suppressor genes with different mechanisms: NF1 regulates cell growth through the RAS pathway, while BRCA1 is involved in DNA repair. Mutations in NF1 cause neurofibromatosis type 1 and increase the risk of early-onset breast cancer. However, there is no direct genetic link between NF1 and

BRCA1.[6] Studies indicate that women with NF1 have a 3- to 5-fold higher risk of developing breast cancer, particularly those under the age of 50.[2] The predominant histological variant of breast cancer in NF1 patients is invasive ductal carcinoma.[7] They also appear to present more aggressively, with a 4-11-fold increased incidence of contralateral breast cancer.[8] In this case study patient has a bilateral breast mass, and a biopsy revealed advanced-stage invasive breast carcinoma.

The patient's advanced stage of breast cancer illustrates the significant diagnostic delays often encountered in NF1 patients. The overlapping cutaneous features of benign neurofibromas and potential malignancies can lead to misinterpretation of symptoms by both patients and their healthcare providers. Here, the patient attributed her ulcerative breast lesion to her NF1 condition, leading to a significant delay in seeking prompt medical evaluation. Additionally, more attention and intervention were focused on her distressing respiratory issues, further adding to the delay in considering other possible causes such as malignancies. This case highlights the importance of earlier breast cancer screenings in women with NF1, possibly by the age of 30, much earlier than the general population.[9] According to the National Comprehensive Cancer Network (NCCN) Guidelines (2025), annual mammography is recommended from ages 30, with consideration of contrast-enhanced breast MRI between ages 30 and 50. MRI increases the detection of cancerous lesions that may be missed during mammograms, especially in younger women with dense breast tissue.[10] This case reinforces the need for tailored cancer screening protocols in NF1 patients that consider both genetic predisposition and personal health history. Implementing standardized screening guidelines could facilitate earlier detection and improve outcomes.

Patients with metastatic breast cancer generally have a poor prognosis, with a 5-year survival rate of only 27% in the era before modern targeted therapies.[11] There is inadequate high-level evidence to support surgical excision of the primary tumour solely to increase survival in metastatic breast cancer. A multidisciplinary team approach has been shown to improve management coordination and clinical outcomes in breast cancer care.[11] The principles of breast cancer treatment are similar to those for the general population. In premenopausal women, ovarian function suppression combined with an aromatase inhibitor represents and established endocrine therapy option, supported by large, randomised trials and guideline recommendations. The NCCN Guidelines for systemic treatment of recurrent or metastatic hormone receptor–positive, HER2-negative metastatic breast cancer state that in the presence of visceral crisis - defined by severe organ dysfunction requiring rapid disease control - initial palliative chemotherapy should be considered as first-line therapy. In the absence of visceral crisis, endocrine therapy combined with CDK4/6 inhibitors is generally preferred as first-line treatment.[10] This recommendation is supported by landmark trials such as PALOMA and MONARCH, in which letrozole was commonly used as the aromatase inhibitor backbone, demonstrating significant improvements in progression-free and overall survival.[12,13] However, real-world treatment decisions are often shaped by local resource availability and patient circumstances. In Malaysia, tamoxifen remains an important and practical endocrine therapy option because of its accessibility and affordability, particularly when access to aromatase inhibitors or CDK4/6 inhibitors is limited.[10]

In this case, the patient was managed by a multidisciplinary team approach. She was initially planned for palliative chemotherapy due to a visceral crisis involving the lung, which she refused due to the side effects despite counselling and support for the treatment. Subsequently, treatment with CDK4/6 inhibitors was also suggested, which are commonly used in hormone receptor-positive and HER2-negative metastatic breast cancers, however, she declined this option. Currently, she is receiving Tamoxifen, with close monitoring for disease progression. Despite refusing further treatment, she was counselled to return promptly should she experience symptoms indicative of disease progression.

CONCLUSION

This case emphasizes the critical importance of early and regular breast cancer screening in patients with NF1. Despite multiple healthcare encounters, this patient's

breast cancer was diagnosed at an advanced stage, largely due to delays in clinical detection and underreporting of symptoms by the patient. Patients with NF1 must be informed and educated about their higher risk of breast cancer. Early recognition through modalities such as mammography, breast MRI and routine clinical examinations has the potential to significantly improve outcomes in this high-risk population. Healthcare providers must implement tailored screening protocols and enhance patient education about increased cancer risks associated with NF1. Timely diagnosis and intervention are vital to reducing morbidity and mortality linked to NF1-related breast cancer. Clinicians must maintain vigilance for malignancies in NF1 patients and proactively advocate early and regular breast cancer screenings.

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