DOI: 10.7860/JCDR/2025/77312.21474

Case Report

Oncology Section

Metastatic Breast Cancer in a Patient with Neurofibromatosis Type I: A Rare Case Report Highlighting Aggressive Disease and Management Challenges

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ABSTRACT

Neurofibromatosis Type 1 (NF1) is a genetic condition caused by a mutation in the NF1 tumour suppressor gene and is associated with a high risk of malignancies, especially breast cancer. Individuals with NF1 face an exceptionally high burden of cancer. Breast cancer is of special concern in NF1, with the risk being increased in women younger than 50 years. NF1-associated breast cancer appears to be more aggressive, often presenting as the basal subtype, and has been noted to occur at an earlier age. This case report describes a 45-year-old female with NF1 who was diagnosed with right-sided triple-negative breast cancer. She received adjuvant chemotherapy and radiotherapy but did not follow up regularly. Two years later, she developed widespread metastatic disease in her liver, bones, lungs, and pleura, with imaging revealing extensive metastases and lymphangitic carcinomatosis. Breast cancer in NF1 patients usually develops at a younger age and is more aggressive, as illustrated in this case. Patients with confirmed NF1 should undergo regular screening starting at the age of 30 years, and any suspicious mass should be biopsied. Most cases are basal; hence, discussions in a multidisciplinary tumour board are essential. Neoadjuvant chemotherapy can provide a survival advantage. Given that radiation therapy in NF1 can cause fibrosis and lead to secondary malignancies, its use should be limited wherever possible. This report emphasises the high risk of breast cancer in NF1, the management of the disease, and the necessity of early detection to improve patient outcomes.

Keywords: Cancer screening, Multidisciplinary tumour board, Neurofibromatosis type 1, Triple-negative breast cancer, Tumour suppressor gene

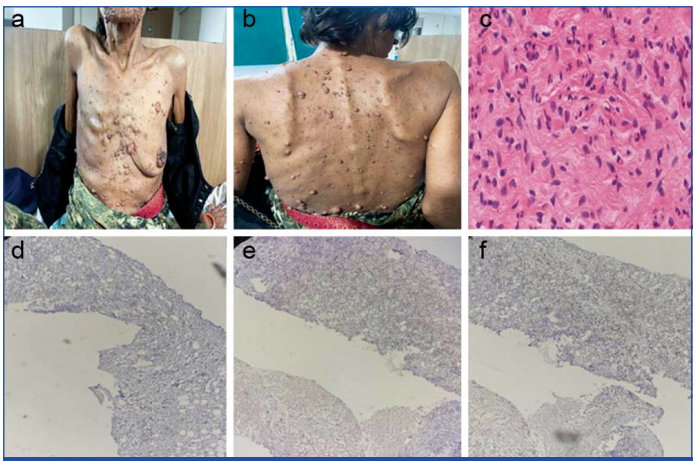
CASE REPORT

A 45-year-old female from Chandrapur, Maharashtra, presented to our clinic with complaints of abdominal pain, joint pain, lower back pain, and constipation over the past month. The symptoms had an insidious onset, were non-radiating, and progressively worsened. Her past medical history included NF1, which was diagnosed 20 years ago [Table/Fig-1a-c]. Two years earlier, she was diagnosed with breast carcinoma, which showed a triple-negative receptor status [Table/Fig-1d-f]. She underwent a modified radical mastectomy at an outside centre without a multidisciplinary tumour board discussion. The tumour size was 5×3×2 cm and showed invasive ductal carcinoma, grade III. Lymphovascular invasion was present, but the margins were clear. Eighteen lymph nodes tested positive, and she was staged as pT2N3a.

Post-surgery, she received four cycles of Adriamycin and Cyclophosphamide, followed by four cycles of Paclitaxel. Adjuvant radiation therapy to the right chest wall and supraclavicular fossa was planned using Three-Dimensional (3D) conformal radiation therapy, delivering a dose of 50 Gy in 25 fractions with the TrueBeam STx linear accelerator.

After a disease-free interval of two years, multiple tiny skin nodules were observed all over her body. The rest of the clinical examination was normal. Laboratory investigations revealed normocytic, normochromic anaemia and an elevated White Blood Cell (WBC) count. Liver function tests showed elevated Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total bilirubin, direct bilirubin, and indirect bilirubin levels. Renal function tests indicated a slightly elevated urea level. Random blood glucose levels were elevated, and vitamin D levels were low. The virology profile was negative.

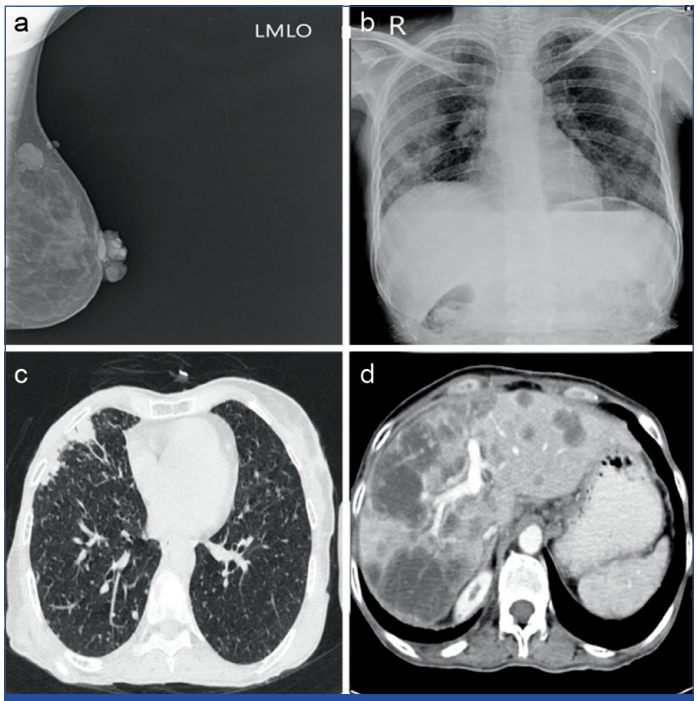
The mammogram of the left breast [Table/Fig-2a] revealed two cutaneous lesions covering the nipple and upper outer quadrant, findings consistent with NF1 [Table/Fig-1c]. An X-ray of the chest revealed opacification in right lung parenchyma [Table/Fig-2b]. Ultrasonography of the abdomen and pelvis showed multiple well-defined rounded hypoechoic lesions with a hyperechoic halo in both liver lobes. Contrast Enhanced Computed Tomography (CECT) of the thorax revealed tiny soft-tissue nodules in the posterior segment of the left lower lobe, the apical segment of the right upper lobe, and the superior segment of the right lower lobe. These nodules displayed a centrilobular distribution arranged in a linear branching pattern with nodular septal thickening in bilateral lung parenchyma.



[Table/Fig-1]: a,b) Multiple hard nodules over the body; c) 40x Haematoxylin and Eosin (H&E) stained microscopic image of the skin nodules showing spindle cells with wavy nuclei without pleomorphism; d) 10x image of immunohistochemistry staining negative for Oestrogen Receptor (ER); e) Negative for the Progesterone Receptor (PR); f) Negative for HER2 receptor.

Irregular homogeneously enhancing soft-tissue thickening of the pleura was observed [Table/Fig-2c], which was associated with nodular septal thickening in the apical and anterior segment of the right lower lobe, as well as the lateral segment of the middle lobe. These findings are indicative of lung and pleural metastases with lymphangitic carcinomatosis.

A CECT of the abdomen and pelvis [Table/Fig-2d] revealed multiple hypodense lesions in the liver, which were peripherally enhancing. It also showed mixed lytic and sclerotic lesions in the bones. A repeat biopsy from the breast lesion was performed, which confirmed a triple-negative Invasive Ductal Carcinoma (IDC). The patient was given palliative radiation for the bone metastases and was started on a single agent, capecitabine, due to poor performance status. Unfortunately, the patient succumbed to her widespread disease two months after initiating therapy.



[Table/Fig-2]: a) Mammogram (mediolateral oblique) showing cutaneous lesions covering the left nipple and upper outer quadrant with no vascular calcifications, no architectural destruction or asymmetry; b) X-ray chest showing white opacification in right lung parenchyma; c) Thorax-Irregular homogeneously enhancing soft-tissue thickening of pleura associated with nodular septal thickening; d) CECT abdomen and pelvis showing multiple hypodense lesions in the liver enhancing peripherally and mixed lytic and sclerotic in the bones.

DISCUSSION

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous condition caused by mutations in the NF1 tumour suppressor gene. It affects approximately 1 in 2,000 to 3,500 people. Individuals with NF1 face a fourfold increased risk of cancer compared to the general population. Complications arising from the disease significantly contribute to morbidity and mortality, with approximately one-third of patients experiencing severe manifestations during their lifetime. Despite familial patterns, the variability in disease expression and the unpredictable onset of complications challenge effective management strategies [1].

Approximately 50% of NF1 cases are inherited, while 50% are due to de novo mutations in the NF1 gene, which codes for neurofibromin. This protein inhibits the Ras oncogene, which stimulates cell growth and division [2-4].

All individuals with NF1 exhibit some degree of neurocutaneous features, including café-au-lait spots, Lisch nodules, and neurofibromas; however, the expression of these features is highly variable and can change with age [2].

According to guidelines from the National Institutes of Health, the diagnosis of NF1 is clinical and can be confirmed if the patient meets two out of seven primary diagnostic criteria: having more than two neurofibromas of any type, two neurofibromas or one plexiform neurofibroma, freckling in the axillae or groin, optic glioma, Lisch nodules, dysplastic changes in the sphenoid bones, or cortical thinning in long bones, or having a first-degree relative with NF1. Additionally, six or more café-au-lait spots larger than 5 mm in prepubertal individuals and larger than 15 mm after puberty are also observed.

Unlike many autosomal dominant conditions, the pathogenesis of NF1 follows a two-hit hypothesis: the first germline mutation in the NF1 gene predisposes individuals to tumour formation, and the second somatic mutation, occurring later in life in specific cells, triggers tumour development [5].This explains the wide range of benign and malignant tumours associated with NF1, such as cutaneous neurofibromas, plexiform neurofibromas, and malignancies like Malignant Peripheral Nerve Sheath Tumours (MPNST). Despite almost 100% penetrance by adulthood, molecular studies suggest occasional incomplete penetrance for pathogenic variants [6-8].

The molecular complexity of the NF1 gene, with its 61 exons and alternatively spliced variants, contributes to the phenotypic diversity of the condition. While many manifestations of NF1, such as freckling and benign neurofibromas, are non-life-threatening, the potential for malignant transformation poses significant challenges. Understanding the interplay between inherited and acquired mutations in NF1 is crucial for optimising diagnosis, surveillance, and management in affected individuals.

Individuals with NF1 face an exceptionally high burden of cancer, including those specific to NF1 and others unrelated to the condition. Common cancers include central nervous system gliomas, MPNST, and rare malignancies like Gastrointestinal Stromal Tumours (GIST) and rhabdomyosarcoma. Studies from Finland, covering the years 1987 to 2012, highlight an increased incidence of these cancers, emphasising the importance of early detection and targeted interventions [9]. Additionally, non-NF1-specific cancers, including breast, digestive, and thyroid malignancies, are also found to be associated with an increased risk of cancer in this population.

Breast cancer is of special concern in NF1, with the risk being increased in women younger than 50 years. The cumulative risk of breast cancer by the age of 50 years in NF1 patients ranges from 7.8% to 8.4%, whereas in the general population, the risk is 2%. The risk declines with age but continues to rise overall. NF1-associated breast cancer appears to be more aggressive and has been noted to occur at an earlier age. Poorer prognostic factors include a higher mortality rate, making management more challenging [1,10].

Molecular studies have shown somatic mutations in the NF1 gene, especially gain-of-function mutations such as gene amplification, which hyperactivate the Ras signalling pathway that drives tumourigenesis. This feature is unique to sporadic breast cancer, in contrast to the germline loss-of-function mutations in NF1 patients. Dysregulated Ras signalling may be a target for therapy that could open up opportunities for pathway-specific interventions; however, further studies in clinical settings are required to explore these targeted therapies further. A comprehensive review of 286 NF1-associated breast cancers showed remarkable age-related variations in the presentation and progression of tumours. Younger patients, with a peak age of 34 to 44 years, presented with advanced-stage disease and developed bilateral or second primary cancers, while slightly better survival was observed in older patients. These results underscore the importance of age-specific surveillance and treatment strategies to address the unique challenges in NF1 patients across different age groups [10,11].

CONCLUSION(S)

This case highlights the significant challenges in managing malignancy in NF1. The 45-year-old patient, who had a history of NF1 and triple-negative breast cancer, presented with significant metastases after a two-year disease-free interval following standard treatment. In this case, the poor outcome may be linked to the absence of early interdisciplinary management and the aggressive nature of the tumour. For patients with NF1, close monitoring, early detection, and well-coordinated treatment are especially important. Moving forward, exploring personalised treatment approaches and ensuring regular follow-up care will be essential to improving outcomes for this vulnerable group.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 14, 2024
- Manual Googling: Mar 13, 2025
- iThenticate Software: Mar 15, 2025 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Dec 11, 2024**
Date of Peer Review: **Jan 20, 2025**
Date of Acceptance: **Mar 18, 2025**
Date of Publishing: **Sep 01, 2025**