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Case Report
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Invasive Carcinoma of Breast in a Patient with Neurofibromatosis Type 1: An unusual association – A case report

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Neurofibromatosis Type 1 is one of the most common genetic diseases in humans, presenting with multiple neurofibromas and an increased risk of developing benign and malignant nerve sheath tumors and central nervous system tumors. However, an association between Neurofibromatosis Type 1 and breast cancer is unknown. We hereby report a case of invasive breast carcinoma of no special type arising in a patient with Neurofibromatosis Type 1.

Keywords: Neurofibromatosis, Type 1, Cancer, Breast, Association

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Introduction

Neurofibromatosis type 1 (NF1) or von Recklinghausen disease is one of the most common genetic diseases in humans, with a prevalence of approximately one case in 3,000 to 4000 births. NF1 is an autosomal dominant disease characterised by multisystem neurocutaneous disorders caused by mutations in the NF1 gene, which is a classical tumor suppressor gene through regulation of Ras guanosine triphosphatase activity, inhibiting GTPase activation, and regulating cell proliferation and differentiation. Those with NF1 mutation are at a fourfold increased risk of developing cancer than the general population.[1]. Multiple neurofibromas, café-au-lait spots, "freckling" in the inguinal and axillary regions and Lisch nodules develop in most affected individuals. Apart from multiple neurofibromas, NF1 patients have an increased risk of developing other benign and malignant neoplasms, including gliomas, malignant peripheral nerve sheath tumors (MPNSTs), juvenile chronic myelomonocytic leukemia, rhabdomyosarcoma, and pheochromocytoma. [2]. NF1 is also a risk factor for the development of breast cancer. 27.7% of all breast carcinomas are said to harbour somatic mutations of the NF1 gene, which are implicated as potential genomic drivers in the development of breast cancer. [3]

Case report

A 45-year-old nulliparous woman known to have Neurofibromatosis Type 1 (NF1) for the last 37 years was referred to us with a left breast mass of six months duration and a cytological diagnosis of breast carcinoma for which she had undergone ten cycles of radiation therapy. She was diagnosed with NF1 at eight years of age. There were multiple neurofibromas all over the body, which gradually increased in number. She had more than six cafe-au-lait spots as well. There was neither any history of significant illness nor a family history of breast cancer or neurofibromatosis.

In the present visit, her vitals, haematological and biochemical parameters were within normal limits. Chest x-ray and abdominal CT scan were also normal. A modified radical mastectomy with axillary dissection was performed. The gross specimen showed multiple neurofibromas in the overlying elliptical piece of skin, the largest one measuring 2.5x2x1.5cms (Fig.1a, b). Axillary pad of fat contained 20 lymph nodes, the largest being 3cms in size. Serial sectioning of the specimen showed areas of fibrosis, and there was no grossly visible tumour. Microscopy showed multiple microscopic foci of residual tumour (invasive duct carcinoma), areas of fibrosis with lymphoplasmacytic infiltrate and cholesterol clefts (Fig.1c, d, e). 17 out of 20 lymph nodes showed metastasis. Histology of the cutaneous nodules was consistent with neurofibroma (Fig.1f). The final diagnosis of residual invasive carcinoma of no special type (NST) with axillary lymph node metastasis (ypT1aN3aMx) and multiple cutaneous neurofibromas was offered.

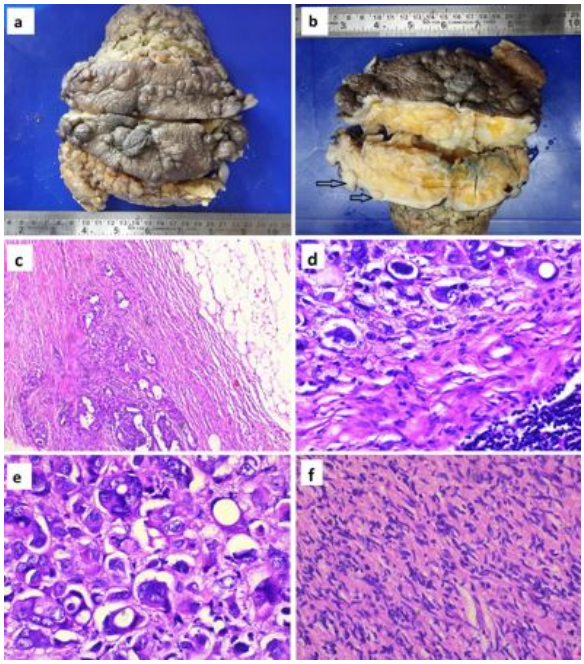

Figure 1.(a) Mastectomy specimen showing multiple cutaneous neurofibromas (b) cut section of the specimen showing neurofibromas (marked) and areas of fibrosis (c-e) microscopy showing breast tissue with invasive carcinoma of no special type (H & E stain) (f) microscopy of cutaneous neurofibroma (H & E stain).

Discussion

NF1 is one of the most common autosomal dominant diseases in humans, caused by mutations in the NF1 gene. It is characterised by multiple cutaneous neurofibromas, cafe au lait macules, Lisch nodules and an increased risk of developing tumors like malignant peripheral nerve

Sheath tumors (MPNST), optic gliomas, rhabdomyosarcomas, leukemias and astrocytomas. However, the association between breast cancer and NF1 is not common in the literature.

Sharif S et al. have shown that younger women with NF1 had five times more chances of developing breast cancer when compared to the general population. 1 Loss of heterozygosity of NF1 gene has been noted in occasional breast cancer cases, which possibly necessitates intensive screening of NF1 patients with ultrasound and magnetic resonance imaging modalities. [2]. The finding of the proximity of both the NF I gene and breast cancer predisposition gene, BRCA 1 on chromosome 17q, supports the association of these two conditions.

Suarez- Kelly LP et al., in their systematic literature review and meta-analysis, have concluded that the mean age at breast cancer diagnosis in NF1 was 49.3 years with a median age of 46 years and an interquartile range of 38.3 to 58.0 years. The majority of the patients were < 50 years of age, with 53% < 50 years old, 28% between 35 and 44 years old and 15% < 35 years old. [3]. Their findings suggested that women with NF1 less than 50 years of age have a five-fold increased risk of breast cancer, increased breast cancer-related mortality and that they present with more advanced disease. [3]. Their review also supported the belief that it may be reasonable to consider NF1 with other hereditary breast cancer syndromes. Early breast cancer screening guidelines need to be extended to include women with NF1. [3].

The presence of a high number of cutaneous neurofibromas can interfere with mammogram interpretation and delay the early diagnosis of breast cancer. [4].

Histopathological types reported are invasive carcinoma - NST, lobular carcinoma and metaplastic carcinoma. Very rarely, male breast cancers in NF1are also reported in the literature. [5].

NF1 breast cancers are often associated with poor survival and unfavourable prognostic factors, such as ER and PR negativity /and HER2 amplification. [6].

Poor prognosis may also be due to presentation at an advanced stage due to delayed diagnosis by the high number of neurofibromas. NF1 patients also appear to have a 4–11-fold higher risk of contralateral breast cancer. [7].

Conclusion

Patients with NF-1 gene mutations appear to harbour a higher overall lifetime risk of any cancer than the general population. Moreover, both the overall mortality and breast cancer-specific mortality seems to be higher among NF1 women. Hence, it is advisable to extend early breast cancer screening guidelines to women with NF1.

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