Abstract
With a prevalence of approximately 1 out of 2,500 to 4,000 births, neurofibromatosis type 1 (NF1), also known as von Recklinghausen’s disease, is one of the most prevalent autosomal dominant diseases in humans. There is four- to five-fold increased risk of malignancy in these patients due to the presence of NF1 gene mutation which is a tumour suppressor inhibiting RAS activation. NF1 is known to be closely associated with central nervous system (CNS) tumours; however, its association with other non-CNS malignancies is not uncommon.

Mutation of BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, susceptibility protein) genes has long been recognized as an important risk factor for the of breast cancer. Incidentally, breast cancer 1 (BRCA1) and NF1 genes are both located in the long arm of chromosome 17. The association between NF1 and breast cancer has long been debated; recent studies, on the other hand, have established this association, with NF1 unequivocally identified as breast cancer susceptibility gene conferring a moderate risk of breast cancer development.

In this report, we described multimodality imaging features related to two female cases of breast cancer with NF1; we further reviewed the literatures on the association between NF1 and breast cancer and its diagnostic challenge.

Keywords: Neurofibromatosis type 1, Breast cancer, Risk factor, MRI
Introduction
Neurofibromatosis type 1 (NF1), or von Recklinghausen’s disease, is an autosomal dominant disease caused by NF1 gene mutation. There is four- to five-fold increase in the risk of malignancy caused by NF1 gene mutation which is a tumour suppressor.\(^1\) It is a disease with complete penetrance but an extremely variable phenotype. In most affected individuals, multiple neurofibromas, which are benign peripheral nerve sheath tumors, café-au-lait spots, “freckling” in the inguinal and axillary regions, and Lisch nodules develop. Apart from that, NF1 patients run 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 gene is located in the long arm of chromosome 17, also interestingly including the BRCA1 gene. The association between NF1 and increased incidence of breast cancer (BC) has been debated for many years; however, more conclusive data have recently confirmed this link.\(^3\) Given all these well-established data, NF1 has been unequivocally identified as breast cancer susceptibility gene conferring a moderate risk of breast cancer development.\(^3\)

Case Reports

Case 1
A 60-year-old woman with NF1 presented with a progressively enlarging painless lump in the left breast for over two months. She denied other medical histories. Her mother, who also had NF 1, died of breast carcinoma at the age of 62. Clinically, there were generalized cutaneous neurofibromas involving the entire body surface including breasts. Breast examination revealed a hard mass in the upper outer quadrant of the left breast, measuring approximately 3 x 3 cm.

Mammogram demonstrated a 3.5 x 3.0 cm irregular spiculated high density mass in the upper mid region of the left breast. There were no associated suspicious microcalcifications. We categorized the lesion as BIRADS 5. Numerous oval circumscribed equal-density lesions also existed bilaterally consistent with cutaneous neurofibromas (Figure 1). Ultrasound showed an irregular indistinct heterogeneous mass with posterior shadowing and internal vascularity, measuring 3.2 x 1.5cm in the upper outer quadrant of the left breast. We did not detect any suspicious axillary lymph node (Figure 2). Magnetic resonance imaging (MRI) showed that the mass was hypointense on T2, had restriction diffusion on DWI with an ADC value of 1.00 x 10\(^{-3}\) mm\(^2\)/s, and demonstrated heterogeneous enhancement with type III curve on the dynamic contrast images. MR spectroscopy demonstrated a high choline concentration peak. These findings were highly suggestive of a breast carcinoma (Figure 3).

Trucut core needle biopsy of the mass revealed desmoplastic stroma filled with malignant cells and arranged in anastomosing trabeculae, consistent with infiltrating ductal carcinoma, Bloom and Richardson Grade 3. Hormone receptor assay was negative for estrogen receptor (ER) and progesterone receptor (PR). The tumour did not show c-erb-B2 overexpression.

Patient underwent mastectomy and axillary clearance three weeks later. We observed cutaneous neurofibromas in the intra-operative specimen of the left breast. The final histopathology was of a poorly differentiated infiltrating ductal carcinoma (Figure 4). No malignant cells were present in the left axillary lymph nodes. Staging CT showed no distant metastases. She recovered uneventfully following the surgery.
Case 2

Our second patient was a 46-year-old woman with underlying learning difficulty and NF1; she presented with a painless lump in the left breast with a duration of more than six months. She did not have other medical histories or family history of breast cancer. Breast examination revealed a large hard mass in the left breast.

Mammogram demonstrated a large irregular spiculated high density mass almost occupying the left upper mid region, measuring approximately 5 x 5cm. This mass is associated with extensive pleomorphic microcalcifications and minimal nipple retraction. We classified the lesion as BIRADS 5. We detected several oval circumscribed low density masses in the left periareolar region, consistent with cutaneous neurofibromas (Figure 5). Corresponding ultrasound showed an irregular indistinct heterogeneous mass with cystic component in the left breast. Another suspicious irregular microlobulated hypoechoic mass was also present in the right breast at the 9 o'clock position (Figure 6). There existed internal vascularity within these masses. We further observed enlarged axillary lymph nodes with loss of fatty hilum bilaterally.

Histopathology from ultrasound guided biopsy revealed Grade 3 medullary carcinoma on the left and Grade 3 invasive ductal carcinoma on the right. Hormone receptor assay was positive for estrogen receptor (ER) and progesterone receptor (PR) with the presence of c-erb-B2 over-expression.

The patient underwent bilateral mastectomy with axillary dissection after the completion of neoadjuvant chemotherapy. Staging CT showed no distant metastases. She recovered uneventfully following the surgery.

Discussion

NF1 is an autosomal dominant inherited disorder with an estimated incidence of 1 in 3000 to 4000 births. There is no gender predilection. Affected individuals run up to 15% additional risk of developing malignancy during their lifetime. Mutation of BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, susceptibility protein) genes has long been recognized as an important risk factor for breast cancer development; incidentally, BRCA1 and NF1 genes are both located on the long arm of chromosome 17. In the past, the association between NF1 and BC was highly debatable; however, over the recent years, many studies have established this association.

The association between NF1 and breast cancer was first reported in 1972; this subsequently led to several similar clinical associations documented in the literature. The largest of these studies identified 58 cases of breast cancer among 3672 women with NF1 diagnosis admitted to National Health Service hospitals in England over the period of 1999-2011. With the increase in age, the relative risk decreased compared to the control cohort: 6.5 amongst women aged 30-39 years, 4.4 in those aged 40-49, 2.6 regarding 50-59 years of age, 1.9 for 60-69, and 0.8 in the subjects aged 70–79 years. Another large study with a cohort of 448 NF1 patients investigated the prevalence of breast cancer and other types of cancer. It showed that the risk of breast cancer was significantly higher in NF1 patients younger than 50 years of age compared with the general population. Sharif et al. found an incidence of 4.6% in NF1 patients who developed breast cancer; however, Madanikia detected 3.2% increased incidence in breast cancer in NF1 women. Given all these well-established data, NF1 has been unequivocally identified as breast cancer susceptibility gene that confers a
moderate risk of breast cancer. This highlights the potential need for a more stringent breast screening protocol in individuals with NF1.

In a study on over 1,000 patients, the breast cancer mortality incidence in NF1 females was approximately 3.5-fold in comparison with the general population. This finding suggests that apart from the increased risk and earlier onset of breast cancer, this subset of patients are also associated with a worse prognosis. The poorer outcome is likely attributed to the increase in triple-negative (ER, PR, and HER2) and HER2-positive tumor subtypes; these subtypes are associated with inferior 5-year survival compared with ER-positive HER2-negative cancers. Uusitalo et al. also reported a significantly higher T stage in patients with NF1 compared with the general population. Our cases were also diagnosed at a later or advanced stage with a T score of higher than two. A study from Manchester confirmed that the adverse outcomes with NF1-associated BC were likely due to aggressive tumor phenotypes and late presentation of patients. We postulate that delayed diagnosis or presentation largely contributes to numerous existing skin neurofibromas, particularly over the chest and breasts, masking the actual breast mass. The most prevalent histopathological type of breast cancer in NF1 and the general population is infiltrating ductal carcinoma, as observed in our cases.

Detecting early breast cancer in NF1 poses a serious diagnostic challenge. Digital mammography is the gold standard for diagnosis in the early disease stages; however, the presence of numerous neurofibromas within the field of view may mask the underlying mass microcalcifications or architectural distortion. Physical examination in these patients may also be inaccurate in view of the amount of cutaneous lesions. MRI is possibly a more appropriate imaging technique, but its reduced specificity versus mammography leads to increased recall rates in the general screening population; this could theoretically be even higher in NF1 carriers. Mammography of subcutaneous neurofibromas affecting the breast shows well-defined benign-appearing masses, often multiple and classically peri-areolar in location. Parts of the outline might be rimmed by air density, reflecting their superficial nature and giving a halo appearance. Sonographically, neurofibromas are usually well-circumscribed hypoechoic masses with posterior acoustic enhancement within the subcutaneous tissue and features similar to a fibroadenoma.

Only one case report by Gokalp et al. was published documenting the MRI appearance of NF1 breast neurofibromas. The author showed that the MRI features of breast neurofibroma depended largely on the histopathological characters, corresponding to areas of cystic degeneration, myxoid matrix, collagen, and fibrous tissue. Neurofibromas are typically low to intermediate signal intensity on T1 weighted sequence and heterogeneous signal intensity on T2 weighted images. The hyperintense regions on T2 weighted sequence correspond to areas of cystic degeneration or myxoid matrix while the hypointense regions represent collagen and fibrous tissues. Hypointense areas on T2 weighted sequence may gradually be enhanced following gadolinium administration.

A malignant contrast enhancement pattern, indistinguishable from IDC, is expected in neurofibromas with sarcomatous changes. Among more than 500 different mutations found in NF1, ductal carcinoma in situ, mucinous carcinoma, squamous cell carcinoma, invasive ductal carcinoma, and lobular carcinoma are among the malignant mutations. Our first patient had invasive
ductal carcinoma while the second had synchronous invasive ductal carcinoma on the right breast and medullary carcinoma on the left one. We found several case reports reporting metachronous contralateral and synchronous bilateral breast cancer which were mainly invasive ductal carcinoma.\textsuperscript{7, 16} Somatic loss of NF1 has further been reported in malignant phyllodes tumors as well as a rare subtype of breast cancer named metaplastic carcinoma.\textsuperscript{7}

To date, there is no literature documenting the MRI features of NF1-associated BC; nonetheless, a case report by Yoon et al. showed non-mass improvement with heterogenous internal enhancement pattern in the affected breast proven to be DCIS with metastatic lymphadenopathy.\textsuperscript{7} We believe that MRI features of NF1-associated breast cancer correspond to its underlying phenotype, with IDC being the most prevalent subtype. The features of breast carcinoma on dynamic contrast-enhanced MRI include spiculated margin, perilesional oedema, architectural distortion, and lymphadenopathy.\textsuperscript{17} As for kinetic enhancement, type II and type III curve are considered suggestive of malignancy. Type II curve is a plateau pattern showing initial increase in signal intensity followed by a flattened enhancement curve. In type III curve, there is washout pattern following a rapid initial increase.\textsuperscript{17} Our patient showed a type III curve enhancement with ADC value of $1.00 \times 10^{-3} \text{ mm}^2/\text{s}$, highly indicative of malignancy. In the study of Tan et al., the cut-off ADC values for benign and malignant lesions were $1.21 \times 10^{-3} \text{ mm}^2/\text{s}$ for $b=500 \text{ s/mm}^2$ and $1.22 \times 10^{-3} \text{ mm}^2/\text{s}$ for $b=1000 \text{ s/mm}^2$, respectively.\textsuperscript{18}

Breast carcinoma with triple-negative phenotype is characterized by poor clinical outcome and high recurrence rate; therefore, it requires a more aggressive treatment.\textsuperscript{19} This disease is not amenable to any endocrine therapy. Treatment for a triple-negative breast carcinoma includes surgery, chemotherapy, and radiotherapy.\textsuperscript{19} Both our patients had mastectomy and axillary clearance and were planned for chemotherapy.

**Conclusion**

In summary, NF1 with breast cancer are associated with a poorer outcome due to various reasons. It is important for both patients and physicians to be aware of the increased risk of breast cancer in the NF1 subset. Invasive ductal carcinoma is still the most common subtype in this population, with imaging findings showing characteristic malignant features. However, in the presence of multiple neurofibromas, particularly in the breast, MRI remains to be a valuable tool for distinguishing between benign neurofibroma compared with other more common benign breast lesions such as fibroadenoma. However, there is considerable overlapping of imaging features in sarcomatous neurofibroma with invasive ductal carcinoma. It is also not uncommon for these patients to present with synchronous or metachronous breast tumor with a different subtype from the primary tumor. The current guidelines used to screen women in general population are not sufficient for screening NF1 patients. We believe that specific screening guidelines are to be designed for earlier diagnosis and reduced morbidity and mortality in women with NF1 and breast cancer.

**Informed Consent**

Both patients consented to the scientific writing of their conditions.

**Funding**

Institutional grant (Grant number: BK006-2018) provided the financial assistance for this case report.

**Conflict of Interest**

None declared.
References


15. Gokalp G, Hakyemez B, Kizilkaya E, Haholu A. Myxoid neurofibromas of the breast: mammographical, sonographical and


**Figure 1:** Case 1- Mammogram (A) Right craniocaudal (CC) view and (B) left craniocaudal spot compression view showing an irregular spiculated high density mass in the mid-region of the left breast. Multiple oval circumscribed equal-density cutaneous neurofibromas were seen bilaterally.

**Figure 2:** Case 1- Ultrasound images showing an irregular, indistinct and heterogeneous mass with posterior shadowing in the left mid-region of the breast. Internal vascularity was seen in the mass on colour Doppler (C). The white arrows showing multiple subcutaneous neurofibromas of varying sizes over the left breast.
Figure 3: Case 1 - (A-B) Axial T2 and T1 weighted breast MRI images showing the irregular heterogeneously enhancing mass in the left mid-region which is hyperintense to the normal fibroglandular tissues. The multiple cutaneous neurofibromas have signal consistent with fat in these two sequences. (C-D) Diffusion weighted (DW) and apparent diffusion coefficient (ADC) images demonstrated that the mass has restriction diffusion with ADC value of $1.00 \times 10^{-3}$ mm$^2$/s, (E) Subtracted dynamic contrast enhanced image showed a heterogeneously enhancing mass with type 3 curve on kinetic analysis (inset) (F) Significant choline peak were demonstrated on the single voxel proton spectroscopy.
Figure 4: Case 1 - (A-B) Intra-operative specimen of the left breast. (C) Haematoxylin and eosin stain photographs under magnification x 100 of the breast carcinoma showed pleomorphic nucleus with increased mitotic activity (black arrow). (D) Haematoxylin and eosin stain photographs under magnification x 100 showed haphazardly arranged spindled cells with wavy nuclei consistent with neurofibroma (black arrow).

Figure 5: Case 2 - (A) Mediolateral (MLO) and (B) Craniocaudal (CC) mammogram views of both breasts showing a large irregular spiculated high density mass occupying the left upper mid region with extensive suspicious pleomorphic microcalcifications. There is mild retraction of the left nipple also seen.
Figure 6: Case 2 - (A-B) Ultrasound images showing an irregular, indistinct and heterogeneous mass with cystic components in the left upper mid-region (A) and irregular microlobulated hypoechoic mass in the right 9 o’clock (B). (C-D) Corresponding CT images of the left breast mass in axial (C) and coronal (D) planes demonstrating a predominantly cystic mass with irregular thickened wall.