Case Report

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Bilateral Breast Cancer with Neurofibromatosis Type 1 Patient: Case Report

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ABSTRACT

Neurofibromatosis type 1 (NF1) is autosomal dominant and it is the most common hereditary disease. This case report is about a woman and her daughter. Both of them are NF1 and mother also has metachronous bilateral breast carcinoma. We analyzed expressions of 84 genes related with DNA Repair by Real Time PCR (AB Applied Biosystem 7000 Sequence Detection System;

Thermo Fisher, Foster City, CA, USA). We also performed NF1 sequencing analyzing in exon 9 of the NF1 gene for mother. In Real Time PCR analysis of DNA Repair Genes, expression chances were predominant both in mother and daughter compared with control group. When the mother and daughter's expression profiles were compared, similar DNA repair array gene expression profiles were observed and the expression of DDB2, MGMT, MLH1, POLB UNG, XPA genes were high in both mother and daughter.

In sequencing analysis, we obtained a mutation in c.1246 C>T. This mutation is reported to be common in NF1 cases with breast carcinoma. Our results indicate that the daughter with NF1 is probably prone to have malignancy in her future life. She should be carefully followed up for early diagnosis of a probable malignancy.

Keywords: Neurofibromatosis type 1, breast cancer, bilateral

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Introduction

Neurofibromatosis type 1 (NF1) is autosomal dominant and it is most common hereditary disease**.** It is considered to be one of the tumor predisposition syndromes (1). Neurofibromin is a protein coded by NF1 gene located at 17q11.2 (2). It is involved in proliferation by affecting intracellular signaling pathways; by hydrolysis of active Ras-GTP, it causes activation of Ras, MAPK, PI3K and mTOR pathways causing proliferation (3).

Not all but some of NF1 patients develop tumors during their life. Neurofibromas, optic gliomas, hamartomas are benign lesions. Loss of heterozygosity in NF1 gene might predispose NF1 patients to certain malignancies such as malignant peripheral nerve sheet tumor, rhabdomyosarcoma, pheochomocytoma, breast cancer, gastrointestinal stromal tumor, neuroectodermal tumors. Additional genetic alterations might be required for their development. In all of NF1 patients with malignancies genetic testing must be performed to understand the mechanism and reason of malignancy association.

Breast carcinoma in NF1 patients was first reported by Borberg et al. (4). Murayama reported 34 NF1 patients with 38 breast cancers (5). Breast cancer among NF1 patients with malignancy is reported about 10-15%, and 18.5% of them occur before the age of 30.

In this paper we aimed to report a mother with bilateral breast cancer and her daughter with NF1 that DNA repair gene expressions and NF1 mutation were analyzed.

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Case Presentation

Patient: In this study, we report of a case of NF1 patient, 44 years old, female. Metachronous bilateral breast carcinoma was observed during follow up. She was diagnosed NF1 at age of 26, she has multiple café au lait spots, neurofibromas and her father also has NF1 disease. She underwent operation left breast excision with axillary dissection because of intraductal carcinoma (comedocarcinoma) and fibrocystic disease in 1996. At that time, there was no lymph node involvement. She was followed up by breast ultrasonography and mammography. Mammography showed BIRADS three lesion in right breast at 2007. In 2009, right breast was observed as BIRADS four. In 2012, right breast mammography showed BIRADS 5 and right breast biopsy demonstrated an invasive ductal carcinoma (modified Bloom Richardson in two upper inner quadrants and diffuse intraductal carcinoma (comedo, cribriform, micropapillary) and tumor was positive in two lymph nodes. She underwent modified radical mastectomy and axillary dissection operation to right side. Chemotherapy and radiotherapy were applied. She is now alive on follow up with no recurrence in two years.

Daughter: She has a daughter, 8 years old, with NF1 diagnosis. She has café au lait spots and freckles. She does not have any neurofibromas or any other tumors. She was diagnosed with NF1 when she was 18 months old.

Informed consent was obtained from patients. Peripheral blood was obtained from each case. Mononuclear cells were separated using the Ficoll-Paque density gradient method. DNA (Roche; Mannheim, Germany) and RNA isolation (Macherey Nagel; Düren, Germany) were carried out. After RNA isolation (Macherey Nagel; Düren, Germany) and cDNA converting (NY-X Technic ATC 401 model, San Diego, CA, USA), expressions of 84 genes related with DNA Repair in standard array (Qiagen; SABiosciences PAHS 042, United Kingdom) were determined by Real-Time PCR (AB Applied Biosystem 7000 Sequence Detection System; Thermo Fisher, Foster City, CA, USA) both for mother and daughter. Fold changes comparing with control group (8 cases without any diseases) and comparing with NF1 patient without malignancy were evaluated. On the other hand; for sequence analysis, after DNA isolation, PCR and PCR clean up were carried out, respectively. Later SAP/EXO (Thermo Fisher; Paisley, UK) was carried out and then was passed to the next step which included Big Dye (Thermo Fisher; Paisley, UK) and Big Dye Clean Up. After Big Dye Clean Up, the sequencing for NF1 gene was carried out.

We performed NF1 sequencing and observed that there is a mutation in c.1246 C>T in exon 9 of NF1 gene.

DNA repair array gene expression results showed that when this patient's results compare with the other NF1 patients without malignancy; ATR, CCNO, MLH1, NEIL1, NTHL1, RAD18, RAD 51, XRCC1, XRCC3 genes are overexpressed and ATM, BRCA1, BRCA2, ERCC4, EXO1, FEN1, LIG1, LIG3, MPG, MRE11A, MSH2, NEIL2, PMS1, POLD3, RFC1, SMUG1, TDG, TOP3B genes are down-regulated in this patient (mother).

PNKP, RAD18, XAB2, XRCC3, XRCC4 and XRCC5 genes were down-regulated compared with control group in her daughter. RAD18 was the most down-regulated gene. The daughter has similar DNA repair array gene expression profile with the mother. This might be a clue that she might have malignancy in her future life. BRCA1, BRCA2, DDB2, MGMT, MLH1, POLB UNG, XPA genes might be possible clue for developing breast cancer.

When malign tumor cases compared which are NF1 and without NF1, we observed that DDB2, MGMT, MLH1, POLB UNG, XPA genes were upregulated for each group to control group. This fold change was more than 10 times.

ERCC1(p: 0.015) and TREX1(p: 0.026) genes were down-regulated when the patient's results compared with the child and they were statistical significance in these 84 genes (Mann-Whitney U Test).

- TREX1: dauhter: 0.142 ± 0.108 (0.078-0.346)
- TREX1: mother: 0.062±0.026 (0.015-0.090)
- TREX1: dauhter: 0.069±0.065 (0.020-0.197)
- TREX1: mother: 0.021±0.006 (0.016-0.032)

Discussion and Conclusion

In this paper, we reported a mother and her daughter case with NF1 diagnosis. The mother suffered from bilateral metachronous breast cancer. DNA repair gene expressions were evaluated for both. The daughter has similar DNA repair array gene expression profile with the mother which was thought to be a clue that she might have malignancy in her future life.

Patil and Chamberlain reviewed the literature for neoplasm associated with germline and somatic NF1 gene mutations (6). Treatment is the same with sporadic breast cancer cases.

Malignancies in NF1 patients are reported to occur at an earlier age than their sporadic counterparts and they have poorer prognosis.

There are more than 500 different NF1 mutations, besides mucinous carcinoma, ductal carcinoma in situ, and squamous cell carcinoma has both invasive ductal carcinoma or lobular carcinoma of breast might be observed in NF1 cases also been reported. In our case the previously observed left breast cancer was intraductal carcinoma and the other breast showed invasive ductal carcinoma 9 years later. The additional genetic alterations in NF1 patients with breast cancer have not been defined yet.

BRCA1 mutation has been demonstrated in some of NF1 associated breast cancer cases. In this study we found that there was a mutation in NF1 gene, c.1246 C>T in exon 9 and BRCA1 and BRCA2 gene expressions were down-regulated. This mutation in NF1 is already available in the literature (7). The altered expression evident in the present mother case might show us that this kind of alterations in combination with a mutation c.1246 C>T might lead to breast cancer.

The other point is that the increase observed in expression of DNA repair genes. Our results point to a shift in the phenotype towards. The DNA repair genes expression had not been studied in any NF1 patients before in the available English-language literature.

In conclusion; we here report a mother and her daughter who both have NF1. The mother had bilateral metachronous breast cancer and NF1 c.1246 C>T mutation. DNA repair gene expressions were similar in mother and daughter. By this reason, we think that the daughter might also have breast cancer in her future life. The DNA repair gene expression decrease or loss might be predictor for cancer susceptibility in NF1 patients. We conclude that NF1 patients might be screened for DNA repair gene expression status to guess possible malignancy.

Informed Consent: Written informed consent was obtained from patients in this study.

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