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Case Report

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Novel Germline Mutation of *BRCA1* Gene in a 56-Year-Old Woman with Breast Cancer, Ovarian Cancer, and Diffuse Large B-Cell Lymphoma

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We report a case of a 56-year-old woman with breast cancer, ovarian cancer, and diffuse large B-cell lymphoma with a *BRCA1* gene mutation. Evidence is mounting that there is a large increase in the risk for hematologic malignancies among patients with genetic changes in the *BRCA* pathways. The genomic analysis demonstrated a frameshift mutation in the *BRCA1* gene: 277_279delinsCC (Phe93fs). It is a novel *BRCA1* mutation that has never been reported, and caused malignant lymphoma as well as breast and ovarian cancer.

Key words
BRCA1 gene, Breast neoplasms, Lymphoma, Ovarian neoplasms

Introduction

Breast cancer is the second most common cancer in Korean women and is expected to continually increase [1]. Hereditary breast cancer accounts for 5%-10% of total cases. Most hereditary breast cancers are associated with mutations in the *BRCA1* and *BRCA2* genes [2], which confer high susceptibility to familial breast and/or ovarian cancer [3,4].

Associated with hereditary breast/ovarian cancer, the *BRCA1* is the most extensively studied cancer susceptibility gene. Germline mutations of *BRCA1* gene result in a predisposition for developing early-onset breast and ovarian cancer with penetrance as high as 85% and 65%, respectively [5]. The protein products of the *BRCA1* gene regulate, at least in part, transcriptional activation, DNA repair, cell-cycle checkpoint control and chromosomal remodeling [6]. About 1,500 genetic variants of *BRCA1* are described in the Breast Cancer Information Core (BIC). A recent meta-analysis reported a large increase in the risk for hematologic

Table 1. Genomic analysis for *BRCA1* and *BRCA2* mutations

Gene	Exon	Nucleotide change	Amino acid change	Zygosity	Mutation type	Mutation effect
BRCA1	6	277_279delinsCC	Phe93fs	Hetero	FS	NR
	11	2082C>T	Ser694Ser	Hetero	Syn	P
	11	2311T>C	Leu771Leu	Hetero	Syn	P
	11	2612C>T	Pro871Leu	Hetero	MS	P
	11	3113A>G	Glu1038Gly	Hetero	MS	P
	11	3548A>G	Lys1183Arg	Hetero	MS	P
	13	4308T>C	Ser1436Ser	Hetero	Syn	P
	16	4837A>G	Ser1613Gly	Hetero	MS	P
BRCA2	2 (5′ UTR)	–26G>A	-	Hetero	IVS	P
	10	1114C>A	His372Asn	Homo	MS	P
	10	1176C>T	Ala392Ala	Hetero	Syn	P
	11	3396A>G	Lys1132Lys	Hetero	Syn	P
	11	3807T>C	Val1269Val	Hetero	Syn	P
	14	7242A>G	Ser2414Ser	Hetero	Syn	P
	17 (Int16)	7806-14T>C	-	Hetero	IVS	P

FS, frameshift mutation; NR, not reported; Syn, synonymous; P, polymorphism; MS, missense mutation; UTR, untranslated region; IVS, intervening sequence.

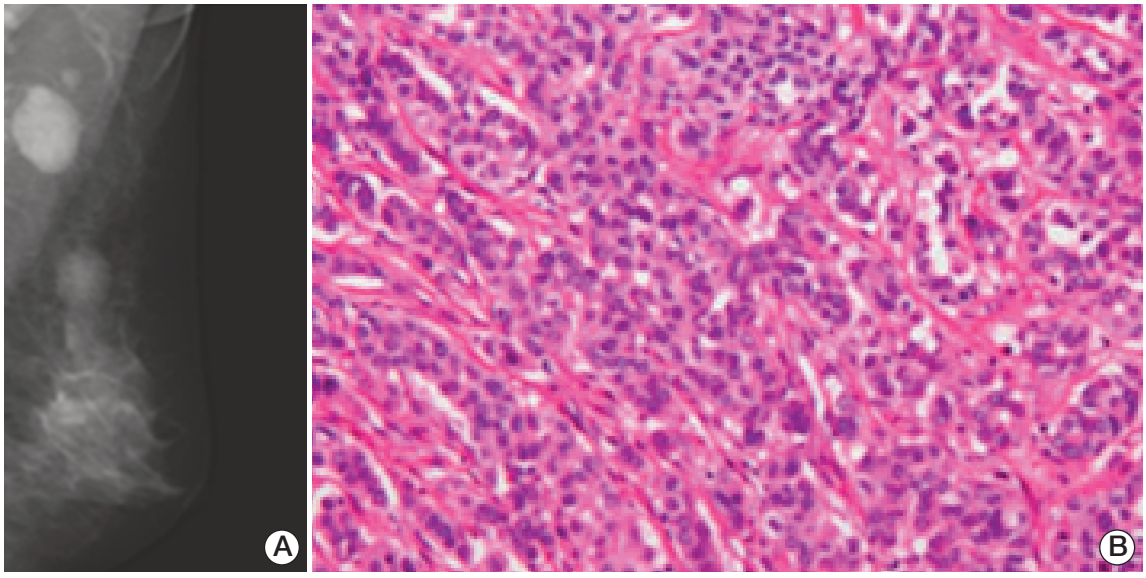

Fig. 1. Radiologic and histologic features of the tumors. (A) The medial lateral oblique mammogram of the left breast shows 2×1.7-cm-sized oval shaped isodense mass with partially obscured margin at upper outer quadrant and 3.4×2.3-cm-sized enlarged axillary lymph node with loss of radiolucent fatty hilum at left axilla. (B) Invasive ductal carcinoma of breast (nuclear grade 2, histologic grade 2) reveals irregular infiltrative nests of tumor cells (H&E staining, ×200).

malignancies among patients with the genetic changes in *BRCA* pathways [7].

We report a case of a 56-year-old woman with breast cancer, ovarian cancer and diffuse large B-cell lymphoma with a novel *BRCA1* gene mutation that has never been reported.

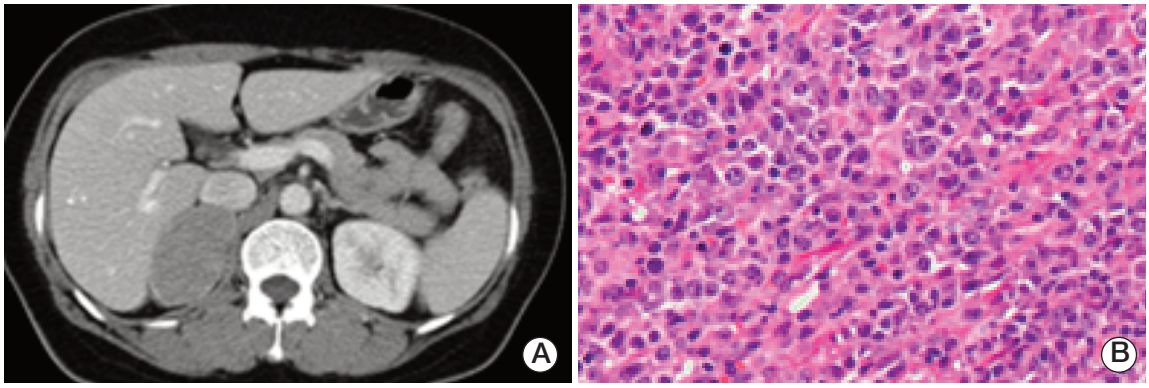

Fig. 2. Abdomen computed tomography shows well defined homogeneously hypodense 5.4×3.7-cm-sized mass in right adrenal gland (A), and diffuse large B-cell lymphoma of adrenal gland shows diffuse proliferation of large atypical lymphoid cells with vesicular nuclei and multiple prominent nucleoli (B) (H&E staining, ×400).

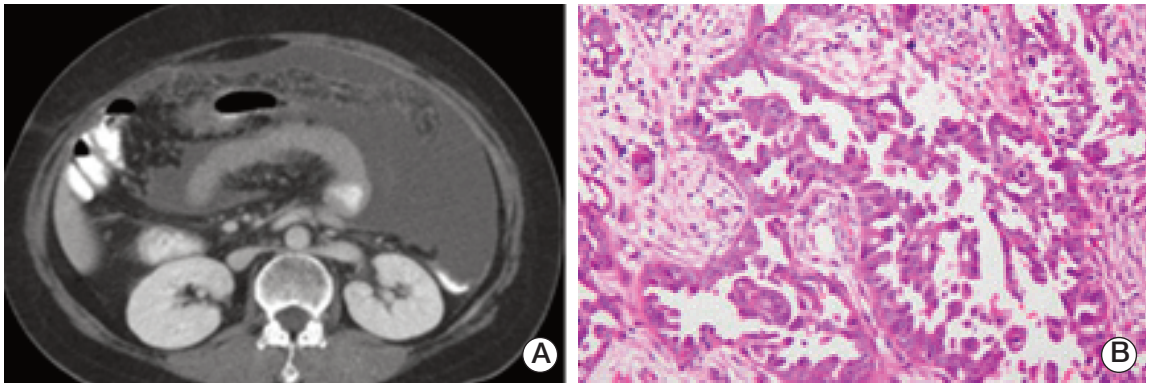

Fig. 3. Abdomen computed tomography shows massive ascites with peritoneal thickening (A) and serous carcinoma of ovary reveals infiltrative tumor nests with papillary features (B) (H&E staining, ×200).

Case Report

A 56-year-old woman was referred to Korea University Anam Hospital for further management for recurred ovarian cancer. The patient was diagnosed with invasive ductal carcinoma in the left breast in 2005 (Fig. 1A). She had undergone modified radical mastectomy and axillary lymph node dissection. A right adrenal mass was incidentally found during staging work up (Fig. 2A), and a right adrenalectomy was done simultaneously with the mastectomy.

Breast tumor pathology confirmed stage IIB invasive ductal carcinoma (T2pN1M0) (Fig. 1B), and the tumor was negative for estrogen receptor, positive for progesterone receptor, and negative for HER-2 overexpression. The 5.4×3.7-cm-sized adrenal mass was confirmed as diffuse large B-cell lymphoma (stage IA) (Fig. 2B). After the operation, she received chemotherapy with a CHOP regimen for four cycles. Adjuvant radiotherapy was applied to the left breast, left chest wall, and right adrenalectomy site. The patient continued tamoxifen from 2006 to 2010, but was lost to follow-up.

In 2011, the patient visited the hospital with abdominal discomfort. Abdominal computed tomography scan showed massive ascites with peritoneal thickening (Fig. 3A). Cytologic analysis for ascitic fluid revealed clusters of adenocarcinoma cells. Thus, she underwent both salpingo-oophorectomy, and pathology confirmed poorly differentiated, bilateral ovarian papillary adenocarcinoma (stage IV) (Fig. 3B). She received chemotherapy with docetaxel (60 mg/m^2) and carboplatin (area under the curve, 6) every three weeks, and achieved a complete remission after six cycles of treatment. However, about six months later, she was referred to Korea University Anam Hospital for the management of

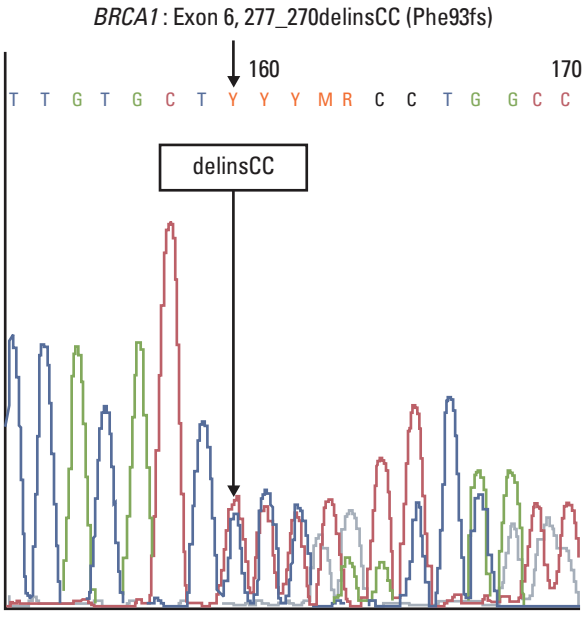

Fig. 4. Genomic analysis demonstrated frameshift mutation in *BRCA1* gene: 277_279delinsCC (Phe93fs).

recurring ovarian cancer. With the second line chemotherapy using gemcitabine and carboplatin, she is in complete remission as of July 2012.

Since the patient revealed that her younger sister was also diagnosed with breast cancer at age 40, genomic analysis for *BRCA1* and *BRCA2* mutations were performed (Table 1). The genomic analysis demonstrated a frameshift mutation in the *BRCA1* gene: 277_279delinsCC (Phe93fs), a novel *BRCA1* mutation never reported (Fig. 4). There was no mutation detected for the *BRCA2* gene. Genomic analyses for other family members were also recommended.

Discussion

The *BRCA1* mutation plays a significant role in breast and ovarian cancers. Most previous studies on *BRCA1* were carried out in women of European ethnicities. Because of the increasing incidence and early age onset of breast cancer in Asian women, studies to determine the prevalence and penetrance of *BRCA1* and *BRCA2* mutation in Asian populations are under way in many Asian countries including Korea [8-10].

A study of 21 Korean hereditary breast/ovarian cancer families identified five deleterious mutations in the *BRCA1* gene; two frameshift and three non-sense mutations, without polymorphisms or unclassified variants [10]. Frameshift mutations were 4159delGA and 5221delTG, which produced a truncated protein signal at codons 1354 and 1714. Three non-sense mutations were 3459G>T (E1114X), 4014C>T (Q1299X), and 5563G>A (W1815X).

An interim report of the Korean Hereditary Breast Cancer (KOHBRA) study was recently published [11,12]. The investigators of the KOHBRA study prospectively estimated the prevalence of *BRCA* mutations among Korean breast cancer patients with high risk for genetic changes. Among 853 probands, 167 mutation (19.6%) carriers were identified. The prevalence of the *BRCA* mutation was 24.8% for breast cancer patients with a familial history of breast/ovarian cancer and 11.3% for patients with early-onset (< 35 years) breast cancer without a familial history. They identified 33 types of *BRCA1* mutations in 68 cases. The most frequent mutations in *BRCA1* gene were 509C>A and 5615_5625 del11insA, where each was found 11 times.

In our case, a frameshift mutation in the *BRCA1* gene: 277_279delinsCC (Phe93fs) was noted. This novel *BRCA1* mutation is not reported in the literature. The patient's breast cancer and subsequent ovarian cancer and her sister's early breast cancer might be affected by this genetic change. This novel *BRCA1* mutation is thought to be related to hereditary breast/ovarian cancer. Of note, our patient exhibited simultaneous diffuse large B-cell lymphoma when she was diagnosed with breast cancer. Unlike the relationship between *BRCA1* mutation and breast or ovarian cancers, the role of *BRCA* in the pathogenesis of malignant lymphoma has not been established. However, there are several studies supporting the hypothesis that *BRCA1* mutation affects the development of hematologic malignancies through defective DNA repair pathways. In a meta-analysis [7], there was a large increase in the risk of hematologic malignancies in patients with mutant genes in the *BRCA* pathway; mantle cell lymphoma, acute myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, and prolymphocytic leukemia. *BRCA1* deficiency was strongly associated with both *de novo* and therapy related acute myeloid leukemia in the study. Some epidemiologic studies [13,14] also found increased risks for leukemia/lymphoma in identified *BRCA1* or *BRCA2* mutation carriers. Moreover, recent study on polymorphisms in DNA repair pathways reported increased risk of diffuse large B-cell lymphoma in *BRCA1* mutant patients [15].

These data suggest that a family history of hematologic malignancies, in addition to breast/ovarian cancers, could be used to determine eligibility for mutation testing of *BRCA1*/*BRCA2* in breast cancer patients. The significance of *BRCA1* mutation in the pathogenesis of malignant lymphoma and other hematologic malignancies should be further investigated.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

References

1. Ko SS; Korean Breast Cancer Society. Chronological changing patterns of clinical characteristics of Korean breast cancer patients during 10 years (1996-2006) using nationwide breast cancer registration on-line program: biannual update. J Surg Oncol. 2008;98:318-23.
2. Robson ME, Boyd J, Borgen PI, Cody HS 3rd. Hereditary breast cancer. Curr Probl Surg. 2001;38:387-480.
3. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71.
4. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-92.
5. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet. 1995;56:265-71.
6. Kerr P, Ashworth A. New complexities for BRCA1 and BRCA2. Curr Biol. 2001;11:R668-76.
7. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 2007;7:152.
8. Ahn SH, Hwang UK, Kwak BS, Yoon HS, Ku BK, Kang HJ, et al. Prevalence of BRCA1 and BRCA2 mutations in Korean breast cancer patients. J Korean Med Sci. 2004;19:269-74.
9. Hedau S, Jain N, Husain SA, Mandal AK, Ray G, Shahid M, et al. Novel germline mutations in breast cancer susceptibility genes BRCA1, BRCA2 and p53 gene in breast cancer patients from India. Breast Cancer Res Treat. 2004;88:177-86.
10. Khoo US, Chan KY, Cheung AN, Xue WC, Shen DH, Fung KY, et al. Recurrent BRCA1 and BRCA2 germline mutations in ovarian cancer: a founder mutation of BRCA1 identified in the Chinese population. Hum Mutat. 2002;19:307-8.
11. Kang HC, Kim IJ, Park JH, Kwon HJ, Won YJ, Heo SC, et al. Germline mutations of BRCA1 and BRCA2 in Korean breast and/or ovarian cancer families. Hum Mutat. 2002;20:235.
12. Han SA, Park SK, Ahn SH, Lee MH, Noh DY, Kim LS, et al. The Korean Hereditary Breast Cancer (KOHBRA) study: protocols and interim report. Clin Oncol (R Coll Radiol). 2011;23:434-41.
13. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68:700-10.
14. Shih HA, Nathanson KL, Seal S, Collins N, Stratton MR, Rebbeck TR, et al. BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. Clin Cancer Res. 2000;6:4259-64.
15. Chen Y, Zheng T, Lan Q, Kim C, Qin Q, Foss F, et al. Polymorphisms in DNA repair pathway genes, body mass index, and risk of non-Hodgkin lymphoma. Am J Hematol. 2013;88:606-11.