Int J Clin Exp Pathol 2023;16(11):352-356
www.ijcep.com /ISSN:1936-2625/IJCEP0146969

Case Report

Bilateral and synchronous male breast cancer: a case report

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Received October 12, 2022; Accepted July 12, 2023; Epub November 15, 2023; Published November 30, 2023

Abstract: Genetic mutational characterization of synchronous bilateral male breast cancer (BC) has been poorly reported due to its rarity. Herein, we present a 55-year-old male patient who was diagnosed with bilateral breast cancer (BBC) and harbored different gene mutations. The diagnosis of synchronous bilateral breast cancer (SBBC) was made using ultrasonography, magnetic resonance imaging (MRI), mammography and core-needle biopsy. Subsequently, bilateral modified radical mastectomies were performed, and histopathologic examination revealed invasive ductal carcinoma. To further investigate the genetic profile of the patient, the biopsy tissue from both breasts and a blood sample were subjected to targeted next generation sequencing (NGS). The genomic profile of the left breast (LB) sample revealed two copy number variations (CNVs), amplification of MCL1 and DAXX, while the right breast (RB) sample showed no obvious mutation. We are reporting this case along with its clinicopathologic findings and genetic investigations, since SBBS occurs extremely rarely, especially in men. The heterogeneity in gene mutations observed in this case may suggest a different pathogenesis and the need for different therapy strategies.

Keywords: Synchronous, bilateral, male breast cancer, NGS, gene profiling

Introduction

Male breast cancer (MBC) is a rare disease, accounting for only 1% of all BC, and synchronous bilateral MBC is even rarer [1, 2]. Due to its rarity, there is limited clinical research on MBC, making it challenging to determine the optimal therapeutic strategy. As a result, treatment approaches for MBC are often extrapolated from data obtained in females [3].

Gene mutation testing (such as BRCA1/BRCA2 mutation testing) has become an important part of cancer management. It helps doctors personalize treatment decisions based on the specific gene mutations driving the cancer. Herein, we present a 55-year-old Chinese male patient with SBBC, and report the genetic characteristics of both breasts through NGS.

Case presentation

A 55-year-old man was admitted to our hospital due to bilateral breast masses and right nipple discharge persisting for three years. The patient had no family history of cancer but had a medical history of multiple gastrointestinal polyp resection in May 2013. Physical examination revealed a 10 × 10 mm mass in the LB and a mobile, nontender 30 × 20 mm mass in the RB. A milky discharge was observed from the right nipple upon squeezing, but not the left nipple. No bilateral axillary or supraclavicular lymphadenopathy was noted. Hormone level testing showed an estradiol level of 72.14 pg/ml, which is nearly the highest level observed in women. Further clinical examinations, including ultrasonography, MRI, and mammography were performed. Breast ultrasound revealed two solid lumps in the central and lower outer quadrant of the RB, measuring 15 * 11 mm and 26 * 17 mm, respectively (**Figure 1A**). In the LB, a 12 * 5 mm solid mass was observed in the lower outer quadrant (**Figure 1B**). The lumps were mixed cystic and solid masses, oval shaped, with clear edges, unevenly distributed, and no lymph node (LN) enlargement. Then bilateral

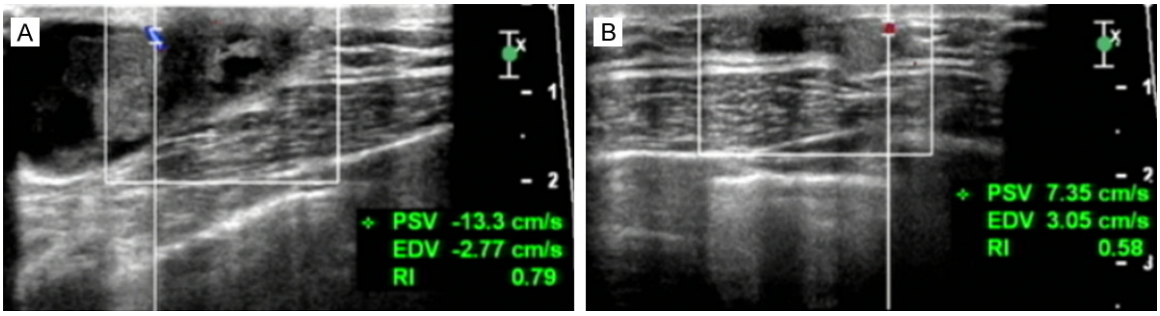

Figure 1. Ultrasonography showed hypoechoic breast lumps (BI-RADS Category 4C) in both breasts. A. Two solid lumps in right breast, measuring 15 * 11 mm and 26 * 17 mm, respectively. B. One solid lump in left breast, measuring 12 * 5 mm.

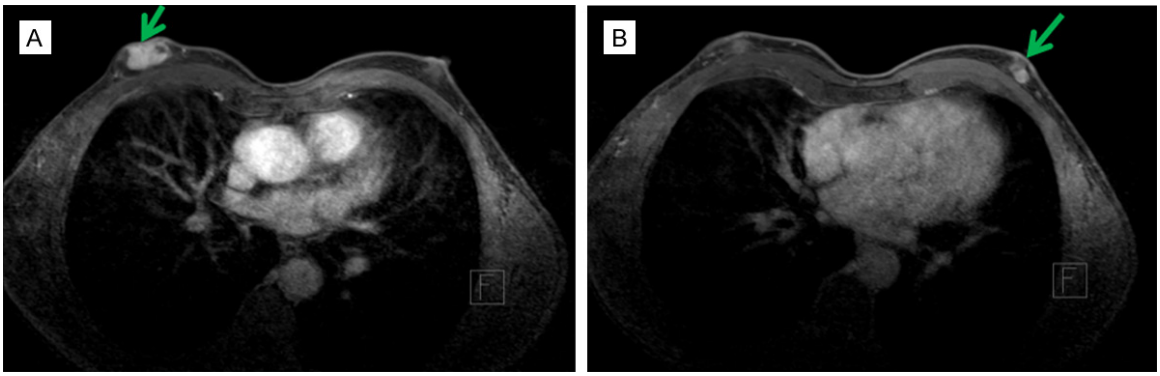

Figure 2. MRI showed solid breast lumps (BI-RADS Category 5) in both breasts. A. Right. B. Left.

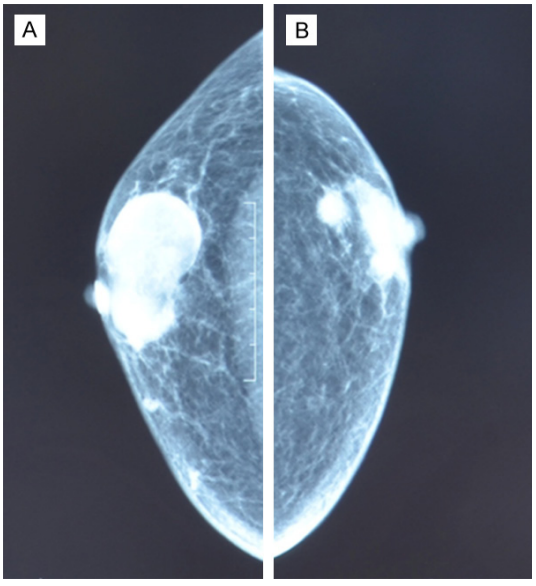

Figure 3. Mammography showed the presence of lumps in both breasts. A. Right. B. Left.

breast MRI (**Figure 2**) and mammography (**Figure 3**) confirmed the presence of lumps in both breasts, measuring 35 * 17 × 26 mm in the RB and 9 * 7 * 13 mm in the LB. Core-needle biopsy revealed partly intracystic papilloma and partly invasive ductal carcinoma in the RB (**Figure 4A**), and invasive ductal carcinoma in the LB (**Figure 4E**). Fine needle aspiration cytology of bilateral axillary LN was negative. Subsequently, bilateral mastectomies were performed. Pathological diagnosis of specimens of the RB revealed a grade IIA, pT2N0M0 stage invasive ductal carcinoma, while the LB specimens demonstrated a grade IA, pT1N0M0 stage invasive ductal carcinoma. Both tumors were classified as Luminal B subtype. Immunohistochemical staining of the RB showed HER2+, progesterone receptor (PR)+, estrogen receptor (ER)+, Ki-67+ and P53+ (**Figure 4A-D**); the left side showed HER2+, PR+, ER+, Ki-67+, P53+ (**Figure 4E-H**). Further FISH testing was negative for HER2 amplification, and BRCA1/2 gene testing was also negative. Adjuvant chemotherapy was administered, consisting of four cycles of epirubicin and cyclophosphamide, followed by four cycles of pacli-

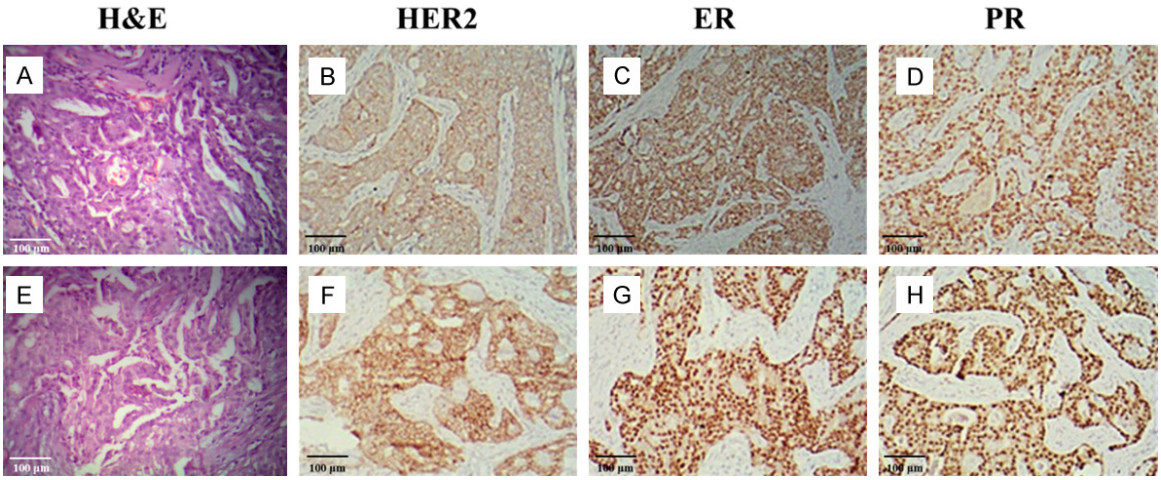

Figure 4. Core-needle biopsy was performed. Samples were used to detect expression of HER2, ER, and PR in both breasts by hematoxylin-eosin (H&E) and immunostaining. H&E stain showed that the right breast (A) and left breast (E) had invasive ductal carcinoma. Immunohistochemistry showed HER2+ (B), ER+ (C), and PR+ (D) in the right breast; HER2+ (F), ER+ (G), and PR+ (H) in left breast.

taxel. No recurrence and metastasis were detected in subsequent examinations. the patients declined further radiotherapy. Hormonal therapy with tamoxifen was initiated, and the patient has remained stable without evidence of progression or recurrence for almost one year.

Addtionally, both the RB and LB surgical tissue samples, along with the blood sample, were subjected to NGS analysis in 3D Medicines Inc., a laboratory accredited by the Clinical Laboratory Improvement Amendment (CLIA) and College of American Pathologists (CAP), The analysis covered the whole coding sequence of 372 cancer-related genes, including single-nucleotide variant (SNV), CNV, and rearrangements. The LB tumor sample had a purity of 75%, the RB tumor sample had a purity of 70%, and the average coverages for the blood sample, the LB, and the RB tumor samples were 477×, 172× and 440×, respectively. The genomic profile of the LB sample revealed two somatic CNVs, amplification of MCL1 (2.5 fold) and DAXX (2 fold). No mutation was found in the RB sample. The genomic profile of the blood sample revealed two heterogeneous germline base substitution mutations, the KMT2C/MLL3 p.Y816fs*1 and the CDKN2A p.E33Gfs*30.

Discussion

KMT2C (Lysine (K)-Specific Methyltransferase 2C) gene encodes KMT2C protein, which is also known as mixed-lineage leukemia 3 (MLL3) [4]. This gene is a central member of the MLL2/3 complex (ASCOM) and possesses H3K4 specific histone methyltransferase activity. Inactivation mutation and abnormal copy number of MLL3 are frequently occurred in leukemia and various solid tumors, such as colon cancer, esophageal cancer, melanoma, lung cancer, and BC. The frequency of MLL3 mutations is reported to be 6-11% in BC according to the TCGA database and 7.9% according to the COSMIC database. Studies have demonstrated that inactivation of the MLL3 results in ureteral epithelial tumors in mice [5], and downregulation of MLL3 by siRNA promotes cell proliferation in HCC cell lines [6]. These findings suggest that MLL3 may function as a tumor suppressor gene. To date, the p.Y816fs*1 mutation has not been reported in breast cancer, but has been detected in colon cancer and melanoma. Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) produces two tumor suppressors, p16INK4a and p14ARF4. p16INK4a binds to and inhibits the expression of cyclin dependent kinases CDK4 and CDK6, thereby blocking them from phosphorylating Rb and maintaining the function of Rb as a tumor suppressor [7]. The deletion or inactivation of p16INK4a leads to an abnormal CDK4/6-Rb pathway and uncontrolled cell cycle regulation [8]. p14ARF functions as a stabilizer of p53 by blocking MDM2-induced degradation of p53, thereby enhancing p53-mediated cell cycle arrest and apoptosis [9]. Mutation or deletion of CDKN2A are frequently reported in a wide variety of tumors,

such as melanoma, glioma, esophageal cancer, stomach cancer, lung cancer, and bladder cancer. According to the COSMIC database, the mutation frequency and copy number loss frequency of CDKN2A in breast cancer are 1.5% and 4.7%, respectively. The CDKN2A p.E33Gfs*30 mutation has not been reported in any cancers yet. Various in vitro and in vivo experiments demonstrated that Paboxilin selectively and sensitively inhibited proliferation of CDKN2A deletion cells [10], indicating that deletion or loss-of-function mutation in CDKN2A may respond to CDK4/6 inhibitor, and Paboxilin has been approved by FDA in treatment of breast cancer.

MCL1 gene encodes an anti-apoptotic protein of the Bcl-2 family, which plays a crucial role in preventing apoptosis [11]. MCL1 is a key regulator of apoptosis. Phosphorylation of MCL1 leads to its interaction with FBW7, a tumor suppressor protein. In patient-derived tumor cells with loss-of-function mutations in FBW7 or lacking FBW7, MCL1 degradation is blocked, resulting in resistant to chemotherapy agents [12]. MCL1 gene copy number gain is commonly observed in leukemia and multiple solid tumors, including BC, lung cancer, colon cancer, and gastric cancer. In breast cancer, the frequency of MCL1 gene CNV is 6.6%, according to the COSMIC database. The protein encoded by Daxx gene possess multiple functions, and is present both in the nucleus and the cytoplasm. It interacts extensively with a variety of molecules, such as centromere protein C, apoptosis antigen Fas, and transcription factor ETS1. It functions as a potent transcription repressor in the nucleus, but may function as regulator of apoptosis in the cytoplasm. Exomic sequencing of non-familial pancreatic neuroendocrine tumors (PanNETs) displayed that 43% of cases harbored mutations in genes encoding either of the two subunits of transcription/chromatin remodeling complex consisting of DAXX and ATRX [13]. DAXX gene CNV widely occurrs in various tumors, such as BC, cervical cancer, liver cancer, and melanoma. DAXX gene CNV frequency is 0.2% in BC according to COSMIC database.

MBC is a rare disease, and SBBC in male patients is even rarer. Several risk factors have been proposed, including radiation exposure, obesity, and testicular disease (orchitis, undescended testis, orchectomy) [1]. However, in this case, no similar risk factors were identified. The prognosis of MBC is a matter of debate. Some previous reports indicate a worse prognosis in men [14], while others claim that the prognosis is similar in male and female patients [2]. The worse prognosis of men is attributed to the unawareness of the disease at an early stage. However, when stages and ages are matched, the prognosis in men and women is the same [15]. MBC is more likely to test positive for hormonal receptors but less likely to be HER2 positive [16]. Specifically, 80-90% MBC are ER-positive, and 73-81% PR-positive, even higher than those in women (75% and 65%, respectively). Therefore, endocrine manipulation such as tamoxifen is a reasonable treatment option for MBC. Some researchers demonstrated therapeutic effect of aromatase inhibitors in MBC. However, unlike in postmenopausal women, absolute suppression of estrogen may not be achieved through aromatase inhibitor therapy in MBC [17].

Treatment for MBC is extrapolated from data in womendue to the limited number of male breast cancer cases available for clinical research. It is hoped that with the development of next-generation sequencing, more cases will be studied to gain a better understanding of the intrinsic characteristics of synchronous bilateral male breast cancer.

Acknowledgements

Thank the patient and his family for consenting to report this case information.

Disclosure of conflict of interest

None.

Abbreviations

BBC, Bilateral breast cancer; BC, Breast cancer; CAP, College of American Pathologists; CDKN2A, Cyclin-Dependent Kinase Inhibitor 2A; CLIA, Clinical Laboratory Improvement Amendment; CNV, Copy number variations; ER, Estrogen receptor; FISH, Fluorescence in situ hybridization; IHC, Immunocytochemistry; LB, Left breast; LN, Lymph node; MBC, Male breast cancer; MRI, Magnetic resonance imaging; NGS, Next generation sequencing; PR, Progesterone receptor; RB, Right breast; SBBC, Synchronous bilateral breast cancer; SNV, single-nucleotide variant.

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References

[1] Weiss JR, Moysich KB and Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 20-26.

[2] Cutuli B, Lacroze M, Dilhuydy JM, Velten M, De Lafontan B, Marchal C, Resbeut M, Graic Y, Campana F, Moncho-Bernier V and et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995; 31A: 1960-1964.

[3] Rubio Hernandez MC, Diaz Prado YI, Perez SR, Diaz RR and Aleaga ZG. Synchronous bilateral breast cancer in a male. Ecancermedicalscience 2013; 7: 377.

[4] Chang A, Liu L, Ashby JM, Wu D, Chen Y, O'Neill SS, Huang S, Wang J, Wang G, Cheng D, Tan X, Petty WJ, Pasche BC, Xiang R, Zhang W and Sun P. Recruitment of KMT2C/MLL3 to DNA damage sites mediates DNA damage responses and regulates PARP inhibitor sensitivity in cancer. Cancer Res 2021; 81: 3358-3373.

[5] Lee J, Kim DH, Lee S, Yang QH, Lee DK, Lee SK, Roeder RG and Lee JW. A tumor suppressive coactivator complex of p53 containing ASC-2 and histone H3-lysine-4 methyltransferase MLL3 or its paralogue MLL4. Proc Natl Acad Sci U S A 2009; 106: 8513-8518.

[6] Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, Aoki M, Hosono N, Kubo M, Miya F, Arai Y, Takahashi H, Shirakihara T, Nagasaki M, Shibuya T, Nakano K, Watanabe-Makino K, Tanaka H, Nakamura H, Kusuda J, Ojima H, Shimada K, Okusaka T, Ueno M, Shigekawa Y, Kawakami Y, Arihiro K, Ohdan H, Gotoh K, Ishikawa O, Ariizumi S, Yamamoto M, Yamada T, Chayama K, Kosuge T, Yamaue H, Kamatani N, Miyano S, Nakagama H, Nakamura Y, Tsunoda T, Shibata T and Nakagawa H. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet 2012; 44: 760-764.

[7] Kumari S, Singh J, Arora M, Ali MS, Pandey AK, Benjamin M, Palanichamy JK, Bakhshi S, Qamar I and Chopra A. Copy number alterations in CDKN2A/2B and MTAP genes are associated with low MEF2C expression in T-cell acute lymphoblastic leukemia. Cureus 2022; 14: e32151.

[8] Roussel MF. The INK4 family of cell cycle inhibitors in cancer. Oncogene 1999; 18: 5311-5317.

[9] Ozenne P, Eymin B, Brambilla E and Gazzeri S. The ARF tumor suppressor: structure, functions and status in cancer. Int J Cancer 2010; 127: 2239-2247.

[10] Konecny GE, Winterhoff B, Kolarova T, Qi J, Manivong K, Dering J, Yang G, Chalukya M, Wang HJ, Anderson L, Kalli KR, Finn RS, Ginther C, Jones S, Velculescu VE, Riehle D, Cliby WA, Randolph S, Koehler M, Hartmann LC and Slamon DJ. Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clin Cancer Res 2011; 17: 1591-1602.

[11] Sancho M, Leiva D, Lucendo E and Orzaez M. Understanding MCL1: from cellular function and regulation to pharmacological inhibition. FEBS J 2022; 289: 6209-6234.

[12] Wertz IE, Kusam S, Lam C, Okamoto T, Sandoval W, Anderson DJ, Helgason E, Ernst JA, Eby M, Liu J, Belmont LD, Kaminker JS, O'Rourke KM, Pujara K, Kohli PB, Johnson AR, Chiu ML, Lill JR, Jackson PK, Fairbrother WJ, Seshagiri S, Ludlam MJ, Leong KG, Dueber EC, Maecker H, Huang DC and Dixit VM. Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 2011; 471: 110-114.

[13] Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti MA, Velculescu VE, Diaz LA Jr, Vogelstein B, Kinzler KW, Hruban RH and Papadopoulos N. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 2011; 331: 1199-1203.

[14] Salvadori B, Saccozzi R, Manzari A, Andreola S, Conti RA, Cusumano F and Grassi M. Prognosis of breast cancer in males: an analysis of 170 cases. Eur J Cancer 1994; 30A: 930-935.

[15] Borgen PI, Senie RT, McKinnon WM and Rosen PP. Carcinoma of the male breast: analysis of prognosis compared with matched female patients. Ann Surg Oncol 1997; 4: 385-388.

[16] Bloom KJ, Govil H, Gattuso P, Reddy V and Francescatti D. Status of HER-2 in male and female breast carcinoma. Am J Surg 2001; 182: 389-392.

[17] Mauras N, O'Brien KO, Klein KO and Hayes V. Estrogen suppression in males: metabolic effects. J Clin Endocrinol Metab 2000; 85: 2370-2377.