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Case Report

# Pleomorphic/solid lobular carcinoma of male breast with PALB2 germline mutation: case report and literature review

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**Summary**

Male breast cancer (MBC) accounts for approximately 1% of all breast cancers and among these infiltrating lobular carcinomas (ILC) represents only 1-2% of all MBC cases. Pleomorphic invasive lobular carcinoma (PILC) is an aggressive variant of ILC with only eight cases reported until now in males. Up to 10% of MBC cases have a germline pathogenic variant in a predisposing gene such as *BRCA1* and *BRCA2* genes. Mutations in *PALB2* (partner and localizer of *BRCA2*) have been reported in men with breast cancer, with a frequency that ranges from 0.8 to 6.4%, but it has never been reported in male ILC. Here, we report a rare and interesting case of an invasive pleomorphic/solid lobular carcinoma, which carries a pathogenic variant in *PALB2* gene, and a family history of breast cancer without other well defined risk factors for developing this type of neoplasia. In addition, we review the current literature.

**Key words:** male breast cancer (MBC), lobular carcinoma (LC), *PALB2,* germline mutations

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## Introduction

Male breast cancer (MBC) accounts for approximately 1% of all breast cancers, and its incidence has been increasing over the years. The mean age at diagnosis is 5 years later for men than for women, and the risk is about 100 times less common among white men than among white women, and 70 times less common among black men than black women [1-3]. The most common histological subtype is invasive carcinoma of no special type (IBC, NST). Risk factors for MBC are well known and include increasing age [3], black race [2,4] and family history [5] as demographic characteristics, genetic alteration, like mutation in the most well characterized *BRCA1* and *BRCA2* [1], and in other genes like *CHEK2*, *PALB2*, *PTEN* and *TP53* [6-8] and lastly liver disease, increased serum estradiol, Klinefelter's syndrome, gynecomastia, obesity, and testicular abnormalities accounting for hormonal alterations [9-13]. Although infiltrating lobular carcinomas (ILC) account for approximately 12% of invasive cancers in women, this subtype is very rare among men, accounting for only 1 to 2% of total cases of MBC, and this is probably due to the absence of acini and lobules in male breast [1]. Mutations in *PALB2* (partner and localizer of *BRCA2*) have been reported in men with breast cancer, with a frequency of the *PALB2* pathogenic variant (PV) that ranges from 0.8 to

6.4% among families with MBC [14], but they have never been reported in male ILC, in which Carnevali et al. reported germinal mutations in BRCA2 and CDH1 [15]. Pleomorphic invasive lobular carcinoma (PILC) is an aggressive variant of ILC with only eight cases reported until now in males, and today none with associated *PALB2* mutation [16-22]. Here, we report a case of an invasive pleomorphic/solid lobular carcinoma, with a pathogenic variant in *PALB2* gene, and a family history of breast cancer without other well defined risk factors for developing this type of neoplasia.

## Case presentation

A 46-year-old male without a past medical history presented a 4 cm irregular mass in the left breast extending between the two superior quadrants. No nipple discharge or itch-sensation in the skin was reported. Family history of the patient revealed a previous breast cancer in his mother at the age of 68 years, brain cancer in his maternal grandmother at the age of 88 years and colorectal and lung cancer in his father, who died at 62 years. The patient subsequently underwent an ultrasound exam of the lump and a breast biopsy. Histopathologically, core biopsies revealed a neoplasia composed by cells with abundant eosinophilic cytoplasm and pleomorphic nuclei, with prominent nucleoli and high mitotic count and some apoptotic bodies, with areas of necrosis (Fig. 1). Immunohistochemically, the neoplastic cells lacked E-cadherin expression, were estrogen (ER) and progesterone receptor (PrG) (Tab. I) positive and showed high proliferation index (Ki-67 70%) (Fig. 1). Human epidermal growth factor receptor 2 (HER2) score was 2+, but the gene was not amplified at silver in situ hybridization (SISH) analysis (Fig. 1). The interdisciplinary team planned a simple mastectomy with homolateral sentinel lymph node biopsy. The treatment was mastectomy with sentinel lymph node biopsy.

On the surgical sample the breast lump was 4 cm in greatest diameter and the histological examination

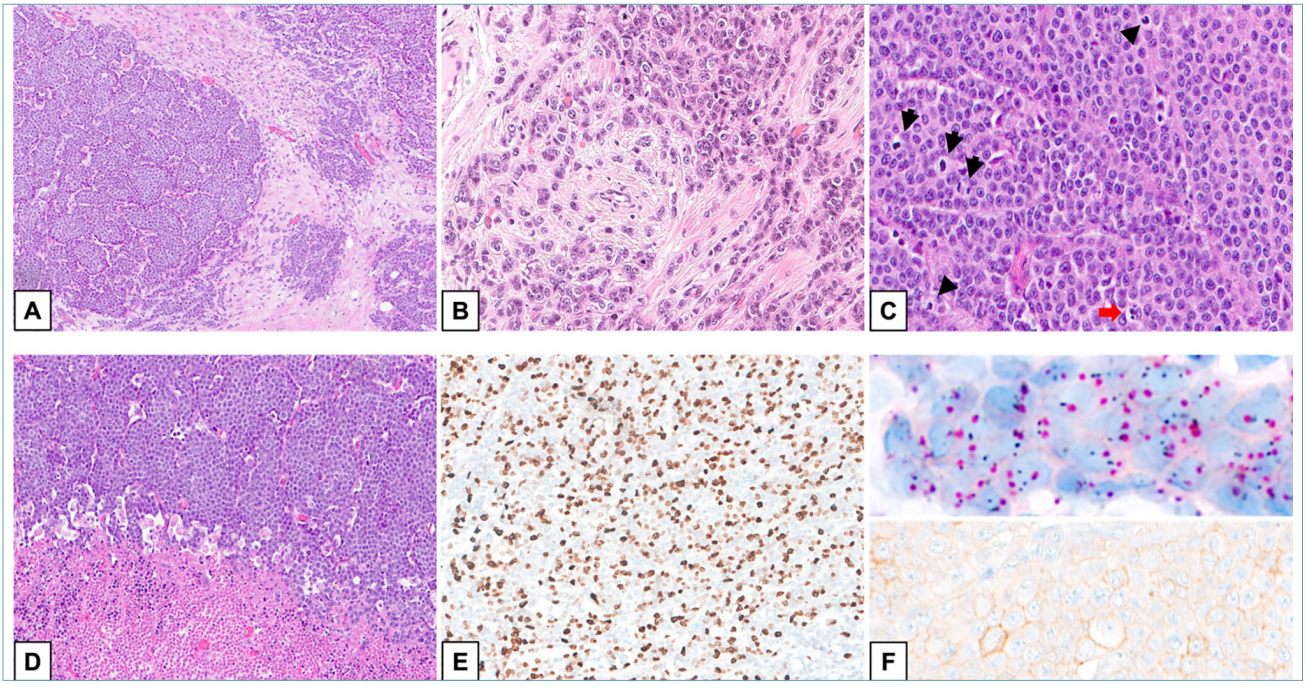


**Figure 1.** Histological and immune-molecular examination. Histological examination on the left breast tumor showed a subcutaneous multinodular neoplasia with infiltrative growth pattern (A, H&E o.m.x100) and tumor cells that have a linear arrangement with encircling of ducts and lobules (B, H&E o.m.x200). They show abundant eosinophilic cytoplasm and pleomorphic nuclei, prominent nucleoli, high mitotic count (black arrows), and some apoptotic bodies (red arrow) (C, H&E o.m.x400). Areas of abundant necrosis was seen within the tumor (D, H&E, o.m.x200). Neoplastic cells showed high proliferative index (Ki-67 70%) (E, o.m.x100) and HER2 expression score 2+, without HER2 gene amplification on SISH analysis (F, lower insert o.m.x400, upper insert o.m.x1000). (Abbreviations: H&E, hematoxylin and eosin; o.m., optical magnification).

**Table I.** Immunohistochemical findings of the present case. Tumor cells lacked immunohistochemical E-cadherin expression and showed high and strong positivity for estrogen (ER) and progesterone receptor (PGR), high proliferative index (Ki-67 70%) and HER2 expression score 2+ without gene amplification on SISH analysis.

| Antibody | Clone | Results | % of positive cells |
|---|---|---|---|
| E-cadherin | 36 | - | 0 |
| ER | SP1 | + | 100 |
| PGR | 1E2 | + | 100 |
| Ki67 | 30-9 | + | 70 |
| c-erbB2 | 4B5 | 2+ | |
| SISH HER2 | VENTANA-ROCHE HER2 Dual ISH | - | 0 |

of the lesion revealed a subcutaneous multinodular mass. The lesion showed, at low power magnification, a focal solid growth pattern, with round and definite margins, and at higher magnification, the neoplasia showed the classic pattern of infiltration of ILC, characterized by the presence of poorly cohesive cells individually dispersed throughout a fibrous connective tissue or arranged in single-file linear cords encircling ducts and lobules. The neoplastic cells are pleomorphic and polymorphic, with hyperchromatic nuclei typically three to four times larger than a mature lymphocyte. One or more nucleoli were sometimes evident. Moreover areas of abundant necrosis was seen within the tumour. The immunohistochemical evaluation demonstrated a lack of E-cadherin expression. According to these results, an ultimate diagnosis of pleomorphic/solid invasive lobular carcinoma (PILC) G3 was made. The prognostic/predictive factors assessment revealed strong positivity for ER and PgR and SISH analysis revealed the absence of *HER2* gene amplification, according to the American Society of Clinical Oncology (ASCO) guidelines 2018[23]. The proliferation index evaluated by Ki-67 was 70% (Fig. 1). The immunophenotype is shown in Table I. Surgical margins of excision were macroscopically and microscopically free from residual cancer. Histological examination of the sentinel lymph node revealed the presence of about 90 scattered tumor cells in the node. TNM staging was pT2 pN0 (i+) (sn) according to American Joint Committee on Cancer (AJCC) 8th edition [24].

On the basis of this histological diagnosis the subsequent treatment was chemotherapy and radiotherapy

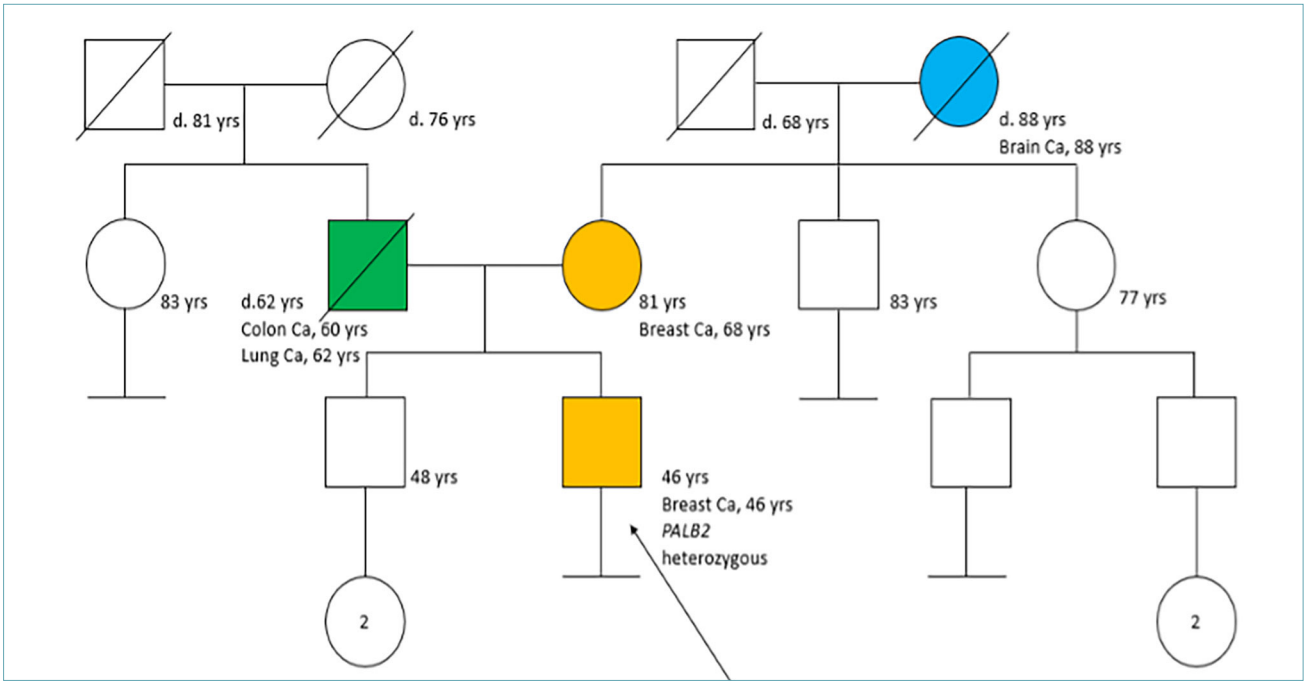


**Figure 2.** Family pedigree. The proband is indicated by black arrow. Brain Ca, brain cancer; Breast Ca, breast cancer; Colon Ca, colon cancer; Lung Ca, lung cancer. Circle, female; square, male; filled symbols, individuals with cancer diagnosis; cross-hatched symbols, affected individuals already deceased; numbers in the circles/squares, number of people of that gender. Abbreviations: Ca, cancer; yrs: age in years; d., deceased.

and the follow-up showed that the patient was disease free at 1 year.

Genetic counseling and karyotype revealed the absence of specific syndromic genetic abnormalities such as Klinefelter syndrome, no previous hormonal or radiation therapy and no other factors that could explain this neoplasm in a man. The genetic risk assessment based on the personal history of male breast cancer and the recurrence of cancer in his family met the criteria for a germline multigene panel on blood sample, after obtaining informed consent, to explain the history of cancer reported in this family. The proband underwent multi-gene testing with the Illumina HBOC NGS kit Hereditary Cancer Solution kit (Sophia Genetics, Tomalab, Milan, Italy).

This panel was developed as a research method to identify genetic mutations associated with inherited breast and ovarian cancers. The panel assesses 11 genes known to harbor mutations related to breast and/or ovarian cancer (ATM, BRCA1, BRCA2, CHEK2, PALB2, RAD51C, RAD51D, NBN, CDH1, SMARCA4, and TP53) (https://www.illumina.com/products/by-brand/ampliseq/community-panels/brca-plus-extended-hereditary-breast-ovarian.html). The result identified a pathogenic variant in *PALB2*, c.1240C > T p.(Arg414*). To date, no other relatives underwent genetic testing (Fig. 2). The p.R414* pathogenic variant, located in coding exon 4 of the *PALB2* gene, results in a C to T substitution at nucleotide position 1240. This change leads to a premature stop codon at position 414 which is predicted to lead to a truncated or absent protein and loss of function.

## Discussion and review of the literature

The male breast usually lacks lobular units and it is thought that for this reason the occurrence of ILC is rare accounting for only 1 to 2% of cases of MBCs [1]. Nevertheless the original concept of ILC and its origin from lobules and terminal unit has been changing over time. The classic definition of ILC considered the distinction between lobular and non-lobular BC based on the presence or absence of lobular carcinoma in situ (LCIS). However, the absence of LCIS in some ILC raise doubt about this concept. According to some authors, the occurrnce of ILC in atrophic breast tissue that has fewer lobules, such as male breast, could be explained by the presence of single pagetoid tumor cells in terminal ducts [25]. Endogenous or exogenous estrogenic stimulation may induce the development of lobules in the male breast and subsequently increases the risk of development of ILC. Risk factors for MBCs are well known and comprise increasing age [3], black race [2,6] and family history[7], genetic alteration, and lastly liver disease, increased serum estradiol, Klinefelter's syndrome, gynecomastia, obesity, and testicular abnormalities[11-15]. PILC is a distinct variant of ILC, first defined in women by Eusebi *et al.* in 1992 [26] which is characterized by higher mitotic count and proliferation index, a greater cellular atypia and pleomorphism and, therefore, a more aggressive clinical course than classic ILC [27]. This variant of ILC has been reported in the male breast, but it is extremely rare with eight cases described to date [15-22], and prognosis and clinicopathological features of this variant in men are less well defined due to its rarity. Table II summarizes our case and the clinicopathological features of the previously reported cases of PILC of the male breast. All cases were in middle-aged or elderly men, with lymph node metastases in 4/9 cases (44.4%) and distant metastases in 1/9 cases (11%). Estrogen receptor expression was almost always present except for the first case reported by Murzabdillaeva et al. Our case showed the absence of *HER2* gene amplification as in all the others reported in the literature. Almost all cases described had some risk factors, the most common was gynecomastia, followed by family history of breast cancer and hormonal factors like alcohol abuse and hormonal therapy for prostatic carcinoma or prostatic hyperplasia. In one of the cases reported the patient had a BRCA2 mutation and in the same case the authors described the presence of an associated Paget disease [22]. Genetic evaluation for germline mutation in our case demonstrated the presence of *PALB2* p.R414* pathogenic variant, located in coding exon 4 of the *PALB2* gene, results in a C to T substitution at nucleotide position 1240. Up to 20% of MBC cases are estimated to have a family history of breast or ovarian cancer and up to 10% of cases had a germline pathogenic variant in predisposing gene such as *BRCA1* and *BRCA2* [28,29]. The frequency of *PALB2* (partner and localizer of BRCA2, OMIM #610355) PV has been described in several studies ranging from 0.8 to 6.4% among families with MBC [14]. In a recent Italian study, *PALB2* represented the most frequently mutated gene (1.2%) among 503 non-*BRCA1-2* MBC patients [30]. *PALB2* is localized on chromosome 16p12.2 and encodes a protein that has an important role in homologous recombination (HR) and DNA double-strand break (DSB) repair [31]. The estimated risk for MBC by the age 80 in *PALB2* mutation carriers has been reported to be 1% compared with a general population risk of less than 0.1% [32]. Among female carriers of germline pathogenic/likely pathogenic (P/LP) variants in *PALB2*, the nature of the variant (truncating vs missense variant), the family history of cancer, polygenic score and other factors influence

breast cancer risk, ranging from moderate to high [33-35]. PALB2 genetic testing should be proposed to MBC patients and to subjects and families with a diagnosis of a typical tumor of the BRCA2 spectrum [36].

Further studies might improve the impact of these factors in MBC risk among carriers of P/LP variants in *PALB2* gene and might define the surveillance options and therapeutic prospective for *PALB2* germline carriers of pathogenic/likely pathogenic variants [35,36]. This is the first reported case of PILC of the male breast with *PALB2* mutation. Yet, the exact pathophysiologic mechanism for the development of male ILC in the breast remains unclear. Additional studies are hence necessary to improve our understanding of this disease in males. This variant is present in population databases (rs180177100, gnomAD 0.003%) and it has been reported in pancreatic, breast and ovarian cancer patients [37-41]. Slater et al. identified three PALB2 germline pathogenic variants, in three families with familial pancreatic cancer, predicted to cause a truncation of the PALB2 protein. One of these families was found to carry the c.1240C > T, p.R414X mutation. This family has four cases of pancreatic cancer and two female breast cancer [37]. Bogdanova et al. reported PALB2 mutation in female patients with bilateral breast cancer and identified in one woman the p.R414X variant [38]. Another group described PALB2 gene alterations in BRCA1 and BRCA2 negative he-

**Table II.** Clinicopathological characteristics of cases of pleomorphic infiltrative lobular carcinomas (PILC) of the male breast previously described in the literature, and of the present case.

| | Maly et al. | Rohini et al. | Ishida et al. | Zahir et al. | Murzabdillaeva et al. first case | Murzabdillaeva et al. second case | Saggini et al. | Costa et al. | Present case |
|---|---|---|---|---|---|---|---|---|---|
| **Year of report** | 2005 | 2010 | 2013 | 2013 | 2017 | 2017 | 2020 | 2022 | 2023 |
| **Age** | 44 | 55 | 76 | 68 | 63 | 79 | 80 | 73 | 46 |
| **Presentation** | 2.5 cm mass | 4 cm mass | 3 cm mass | 2.8 cm mass | Left neck mass, 1.7 cm breast mass with nipple retraction and skin rash | 2 cm mass and skin itchiness | 3 cm erythematous plaque of the nipple | 3.9 cm mass, nipple retraction and skin thickening | 4 cm mass |
| **Genetic mutations** | Not evaluated | Not evaluated | Not evaluated | Not evaluated | Not evaluated | Negative for genetic testing | Not evaluated | BRCA2 mutation | PALB2 germline mutation c.1240C>T p.(Arg414*) |
| **Risk factor** | Grandmothers died of breast cancer | No risk factors | Gynecomastia Progestational agent for prostatic carcinoma for 10 years | Gynecomastia, alcohol abuse | Gynecomastia | No risk factors | Not reported | Obesity, treatment with finasteride for benign prostatic hyperplasia, family history of breast cancer (two nieces) | Mother with breast cancer |
| **Estrogen Receptor** | Positive | Not evaluated | Positive | Positive | Negative | Positive | Positive | Positive | Positive |
| **Progesterone Receptor** | Positive | Not evaluated | Negative | Positive | Negative | Positive | Positive | Positive | Positive |
| **Her2/neu** | Negative | Not evaluated | Negative | Negative | Negative | Negative | Negative | Negative | Negative and not amplified |
| **E-Cadherin** | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| **Lymph node involvement** | None | None | None | pN2a | pN3c | None | Not reported | pN1(sn) | pN0(i+)(sn) |
| **Treatment** | Radical mastectomy with axillary dissection | Radical mastectomy with axillary dissection | Not reported | 4 cycles of chemotherapy | 7 cycles of chemotherapy, radiotherapy | Left simple mastectomy with sentinel lymph node biopsy | Not reported | Left simple mastectomy with nipple excision and sentinel lymph node biopsy, chemotherapy, radiotherapy | Left simple mastectomy with sentinel lymph node biopsy, chemotherapy and radiotherapy |
| **Follow-up** | Disease free at 2 years | Disease free at 1 year | Disease free at 2 months | Disease free at 3.5 months | Brain metastasis | Disease free | Not reported | Not reported | Disease free at 1 year |

reditary breast cancer, and one of the mutations identified was the p.R414X variants [39], which was also described by Casadei et al. in a series of familial breast cancer [40]. Another tumor in which this germline mutation has been highlighted is serous ovarian cancer, associated with other variants of the same gene and with mutations in other genes like BRCA1, BRCA2, CHEK2, BRIP1, BLM, MAP3K15, and PTPRH[41].To date, *PALB2* c.1240C > T has never been described in the literature in male breast cancer patients where other truncating *PALB2* mutations are reported [7,31].

## Conclusions

We investigated the presence of germline mutations in a male patient with a diagnosis of PILC of the breast and identified a pathogenic variant of PALB2 gene, previously not reported in this type of neoplasia.

### Conflicts of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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### Authors' contributions

LC, MA, and DC designed the study. ER, MA and TC drafted the manuscript. ER and TC performed IHC analyses. JF and SDT performed molecular analysis and were responsible for molecular diagnosis. LC, MA, and DC were responsible for histopathological diagnosis. LF was responsible for clinical diagnosis and management. All authors have read and agreed to the published version of the manuscript.

### Ethical consideration

The study was conducted according to the guidelines of the Declaration of Helsinki and performed in accordance with the ethical requirements of biomedical research promulgated by the international and national governments. The patient written informed consent was acquired upon tissue biopsy.

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