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Mutation in CHEK2 and hereditary breast cancer: A case report

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Abstract

Breast Cancer (BC) is the cancer that ranks first in incidence and mortality among women. It is estimated that 5 to 10% of BC cases develop in patients who carry a hereditary predisposition associated with autosomal dominant transmission and high penetrance susceptibility genes. Germline mutations in CHEK2 have been linked to susceptibility to various malignancies, including BC. We present the case of a 57-year-old patient with significant family history of BC, who was diagnosed with localized BC that was hormone receptor-positive and HER2-positive. Given the family history, a basic panel of hereditary cancer CNVs (37 genes) was conducted, revealing the variant c.483_485del; p. (Glu161del) in heterozygosity in the CHEK2 gene (NM-0077194.4), classified as likely pathogenic. Our purpose is to present this case and promote a comprehensive education about genetic and cancer risk in individuals carrying pathogenic or likely pathogenic variants in the CHEK2 gene.

Keywords: Breast cancer; Germline mutation; CHEK2.

Introduction

According to data from the World Health Organization (WHO), Breast Cancer (BC) accounts for approximately 25% of all cancer cases in women and is the most common cancer among women, excluding non-melanoma skin cancers. It is estimated that over 2 million new cases of BC are diagnosed worldwide each year [1].

An estimated 5 to 10% of BC cases develop in patients with a hereditary predisposition associated with autosomal dominant and highly penetrant susceptibility genes. Germline mutations in CHEK2 have been linked with susceptibility to several malignancies, including BC [2,3]. The CHEK2 gene encodes the CHK2 serine/threonine kinase, which is involved in DNA damage response (DDR). Activated by DNA damage, ATM kinase catalyzes CHK2 phosphorylation at position T68, promoting CHK2 homodimerization through its forkhead-associated domains and kinase domain autophosphorylation [3,4]. Activated CHK2 phosphorylates multiple proteins involved in DNA repair and response to DNA damage, including BRCA1/BRCA2 and p53 [5,6]. Although the ATM-CHK2-p53 pathway's role in DNA damage-induced cell cycle checkpoint is redundant, CHK2 participates in p53-dependent cell death [7-10].

The existence of variations in the CHEK2 gene is associated with autosomal dominant inheritance in BC predisposition. In the case of women with pathogenic variants in this gene, their risk of developing BC significantly increases, around 12% compared to the general population. This increased risk is also observed in men. For men, pathogenic variants are also linked with an increased risk of developing familiar prostate cancer [2,11,12].

For these patients, providing genetic counseling about preventive measures and recommended follow-up guidelines for women carrying pathogenic or potentially pathogenic variants in the CHEK2 gene is crucial. Additionally, initiating family segregation studies would be advisable to assess the specific risk in each of the relatives of these patients, who may be susceptible to carrying the detected pathogenic alterations in the CHEK2 gene.

Case presentation

Patient of 57 years old, premenopausal, with personal history of smoking. Family history of a sister diagnosed with breast cancer at 36 years old and a maternal cousin diagnosed with breast cancer at 38 years old.

She presents with a left breast tumor, steadily growing and progressive, painless. On physical examination, a stony mammary tumor of 1.5 cm in the largest diameter was noted. No axillary adenopathies present. Bilateral mammography is performed, revealing a 19 mm nodule with irregular margins in the upper outer quadrant of the left breast; associated with heterogeneous microcalcifications. Diagnostic impression: Suspicious nodule in the left breast. BI-RADS 4C. High level of suspicion.

A core biopsy showed Invasive Ductal Carcinoma (IDC) with final histological grade I, estrogen receptor (ER) positive 90%, Progesterone Receptor (PR) positive 60%, KI 67 35%, HER2 ++ amplified by SISH. Fine-needle aspiration of her lymph node was positive for adenocarcinoma.

A chest and abdominal Computed Tomography (CT) scan and a bone scan were performed, no evidence distant metastatic disease.

Considering the family history, a genetic study is requested. A basic panel of hereditary cancer with CNVs (37 genes) is performed, with results expected in approximately 2 months. The case was discussed by a multidisciplinary tumor board. In a patient with T1N1MO EII ER+ PR+ HER2-positive BC, neoadjuvant therapy with sequential anthracyclines and taxanes associated with trastuzumab is proposed. A mammary and axillary clip is placed, and treatment is initiated.

Upon completion of anthracycline treatment, the results of the genetic study are received. This is a genetic test that analyzes 37 specific genes for Copy Number Variations (CNVs) that could be associated with an increased hereditary risk of developing different types of cancer. CNVs are DNA alterations that affect the number of copies of a gene region and may be linked to a genetic predisposition to cancer. The variant c.483-485del; p.(Glu161del) in heterozygosity in the CHEK2 gene (NM-0077194.4) was detected, classified as probably pathogenic.

The possibility of immediate mastectomy and immediate tissue-expander reconstruction, as well as contralateral prophylactic mastectomy, is discussed with the patient. The patient preferred to undergo left breast-conserving surgery only.

Discussion

CHEK2 is categorized as a gene with a moderate cancer risk. The transmission of cancer susceptibility linked to CHEK2 variants follows an autosomal dominant inheritance pattern, although not all individuals carrying these variants will manifest the disease. The presence of a pathogenic or possibly pathogenic variant in a single allele of CHEK2 (heterozygosity) is associated with an increased lifetime risk for various types of cancer. The most investigated variants in CHEK2 are c.1100delC and c.Ile157Thr (c.I157T). These specific variants have undergone detailed analysis due to their association with an increased risk of cancer in carriers. Variants in CHEK2 that result in protein truncation or changes in the reading frame are correlated with a higher risk of breast cancer (BC). The c.1100delC variant, mainly observed in individuals of northern or eastern European ancestry, is associated with a two to threefold increase in BC risk [13,14]. Data indicate that the cumulative risk of developing BC in women carrying this variant is 6% at 49 years and 32% at 80 years of age [15].

Cumulative lifetime risks for BC associated with variants inducing reading frame changes in CHEK2 range from 15% to 40% and tend to be more pronounced when there are family histories of BC [14,16]. Regarding missense pathogenic variants in CHEK2, the associated cancer risks are not fully elucidated, though they are likely lower than variants resulting in protein truncation. For instance, the c.Ile157Thr variant has been linked only to a modest increase in BC risk (HR 1.58, 95% CI 1.42-1.75) [17]. In another study, cumulative risks of developing BC based on age for the c.Ile157Thr variant were estimated at around 3% at 49 years and 18% at 80 years [15].

In the case of our patient, we have detected the presence of a specific variant in the CHEK2 gene (NM_0077194.4), designated as c.483_485del; p.(glu161del), in a heterozygous state. This variant has been classified as probably pathogenic. What this variant does is alter the resulting protein by deleting a single amino acid in a non-repetitive region, without changing the reading frame. It's worth noting that this variant is already registered in the ClinVar database with identification 141783. However, its interpretation has generated some controversy, being categorized as both a variant of uncertain significance and probably pathogenic. This variant has also been documented in medical literature in cases of patients with BC and/or ovarian cancer [18-23], prostate cancer [24], and pancreatic cancer [25]. Furthermore, this same variant has been found in 5 heterozygous individuals in the gnomAD population database, as well as in a healthy woman registered in the Flossies healthy elderly database. In addition to these findings, in vitro studies have demonstrated that this variant has an impact on the function of the CHEK2 protein. It has been observed to negatively affect protein expression and significantly reduce its kinase activity, as indicated in previous research [26,27]. Based on this information, we have classified this variant as probably pathogenic. It is primarily associated with a moderately increased BC risk, especially in young women, as is the case with our patient. Individuals carrying a CHEK2 mutation have a lifetime risk of developing BC that is higher than the average population, though it remains lower compared to more widely known mutations like BRCA1 and BRCA2.

Although women with mutations in the CHEK2 gene typically receive a BC diagnosis at a younger age than the general population, our patient was diagnosed at 57 years of age. BC associated with this mutation is usually well or moderately differentiated, as in our patient's case. The biological profile of BC with a CHEK2 mutation can vary, but there are some clinical and molecular characteristics that are observed frequently in this context. These tumors are often estrogen receptor (ER) and progesterone receptor (PR) positive, as in our patient's case, and HER2 negative. However, in our patient's case, the BC was HER2 positive [28].

Although these patients have an increased risk of developing bilateral BC, recommendations for prophylactic bilateral mastectomy tend to be more cautious compared to mutations in genes like BRCA1 and BRCA2. This is because the absolute BC

risk associated with CHEK2 mutations is moderate compared to BRCA mutations, and the decision to undergo prophylactic mastectomy should carefully consider the specific benefits and risks for each patient [28].

These patients should receive genetic counseling regarding recommended prevention and monitoring measures for carriers of pathogenic or probably pathogenic variants in the CHEK2 gene. Additionally, the possibility of initiating family segregation studies should be considered to assess the specific risk that each of the patient's relatives may have of carrying the detected pathogenic alteration in the CHEK2 gene. It's important to note that these patients may benefit from more rigorous early detection and surveillance strategies for BC. In some cases, the possibility of implementing preventive measures, such as prophylactic mastectomy, should also be considered, depending on individual risk assessment and relevant medical considerations.

Conclusion

The case of a patient with Stage II BC and significant family history was presented, in which the variant c.483_485del; p.(Glu161del) was identified in heterozygosity in the CHEK2 gene (NM_0077194.4), classified as probably pathogenic. During the discussion, the importance of providing appropriate genetic counseling was emphasized, aiming to empower patients to make informed decisions regarding optimal treatment and surveillance options.

Declarations

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