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CASE STUDIES

Hereditary breast cancer and the need for improvement of screening

Cancerul mamar ereditar: necesitatea screeningului eficient

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Abstract

While hereditary breast cancer only makes up 5% to 10% of all cases, female patients with pathogenic mutations such as BRCA1, BRCA2, CHEK2, etc., are at a higher risk of developing it. Positive family history (such as multiple family members affected by this and other forms of cancer) prompts a more rigorous approach towards the screening and early diagnosis of these patients, as well as a need for counseling for family members.

A 33-year-old female patient was diagnosed with Invasive Ductal Carcinoma NST (No Specific Type) in the left breast, confirmed by biopsy and MRI. Family history revealed early-onset pancreatic cancer (under 65 years old) and was considered as positive, suggesting genetic counseling. We performed the Cancer Risk Test: the patient's results were positive for two genes - BRCA2, which is associated with the risk of breast and pancreatic cancer, and CHEK2, associated with the risk of breast and colon cancer.

Due to the autosomal dominant inheritance model of these genes, the patient's descendants have a 50% chance of developing breast cancer. This high risk indicates early start of screening (through mammography, breast MRI, liquid biopsy) or even preventive surgery (such as postmenopausal removal of ovaries or breasts) in order to prevent or diagnose these patients in a timely manner.

Key words: breast cancer, BRCA, genetic panel, screening

Rezumat

Cancerul de sân ereditar reprezintă 5-10% din formele de cancer mamar diagnosticate. Pacientele purtătoare de mutații patogene, cum ar fi BRCA1, BRC2, CHEK2, prezintă un risc înalt pentru a dezvolta acest tip particular de neoplazie. Istoricul familial pozitiv aduce cu sine suspiciunea unui cancer ereditar, indicând clinicianului nevoia de a investiga aspectul genetic al neoplasmului.

O pacientă în vârstă de 33 de ani este diagnosticată cu carcinom invaziv ductal NST la nivelul sânului stâng, diagnostic confirmat prin biopsie și RMN. Istoricul familial relevă un carcinom pancreatic apărut înainte de vârsta de 65 de ani, fiind considerat pozitiv. Am efectuat panelul Cancer Risk Test, care a fost pozitiv în cazul mutațiilor la nivelul genelor BRCA2 și CHEK2.

Din cauza modelului autosomal dominant de transmitere a acestor gene, descendenții pacientei poartă un risc de 50% de a fi purtători ai mutațiilor, și așadar susceptibili pentru a dezvolta neoplazii asociate (cancer mamar, ovarian, pancreatic, de colon). Riscul înalt indică necesitatea screeningului precoce, atât în ceea ce privește pacienta, cât și succesorii acesteia.

Cuvinte cheie: cancer mamar, BRCA, panel genetic, screening

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Introduction

Breast cancer is the most common form of malignancy in female patients, with a significant impact on the patients' life expectancy and quality of life. Therapeutic management has veered towards conservative measures nowadays - with localized, targeted medicine being able to spare adjacent thoracic structures and enabling the patient to return to day-to-day life and physical activity. However, hereditary breast cancer poses a different set of implications and challenges.

Up to 10% of breast cancers have a hereditary component. This particular cluster of cancers brings forth a myriad of issues for the patient and practitioner alike, regarding therapeutic management as well as screening of family members. Important representatives are the BRCA1 and BRCA2 genes (Lux et al., 2016). These play an important role in tumor supression: inducing DNA damage repair mechanisms, remodeling chromatin and apoptosis (Wu et al., 2010; Shahid et al., 2014). Due to their function, these two genes can also cause other forms of cancer – they are associated with the risk of ovarian cancer and contralateral breast cancer (Kuchenbaecker et al., 2017).

Although the BRCA1 and BRCA2 genes are the hallmark of a large number of breast cancer cases, they are not the only ones that play a role in a patient's diagnosis. Multiple genes are now associated with the risk of developing breast cancer, such as CHEK2, PTEN or TP53 (Van Der Groep et al., 2011).

The case herein presented illustrates the complex nature of hereditary breast cancer and its management. Gaining as much information as possible regarding a patient is a goal for the practitioner - however, is there a limit after which further information becomes counterproductive?

Case presentation

A 33-year-old female patient presented after self-examination revealed a lump in her left breast. She was currently under treatment for depressive disorder. Family history was negative, with the exception of a paternal grandmother, diagnosed with pancreatic cancer at 53 years of age.

The clinical exam showed no pathological elements, excepting a tumor-like formation in the left breast.

The patient was referred to breast ultrasound, which identified a 25 mm lesion in the left breast and enlarged lymph nodes with a prominent cortical area on the left side. The result prompted a biopsy, which showed the following profile: CD NST RE=80% RP=70% Her2=0 Ki67=10%. Contrast MRI was performed, showing an oval lesion with infiltrative margins, heterogeneous contrast, 28 mm in diameter. Two centers with increased contrast uptake were identified, presenting imprecise contours and a 5-6 mm diameter. Left axillary lymph nodes were inflamed.

Considering age and diagnosis, a CANCER RISK test (Gendia-Belgium) - a gene panel investigating 30 genes linked to cancer - was carried out, identifying a heterozygous mutation for BRCA2 c.6567 C>A and a heterozygous mutation for CHEK2 c.902delT.

The final diagnosis was invasive ductal carcinoma, T1N1M0, BRCA2 positive.

Therapeutic management consisted of bilateral radical mastectomy with reconstruction. Neoadjuvant chemotherapy was not performed because of the low value of the proliferation index KI67. In order to decide the next step in therapy, a molecular tumor profile was needed to establish potentially viable chemotherapy plans, potential interactions and prognosis scores. Other systemic therapies such as chemo- or hormonal therapy were not accepted by the patient.

Discussions

Hereditary breast cancer is still a challenge to patient care. For our patient, chemotherapy was proposed as a form of preventive treatment of metastasis due to her young age and her supposedly increased resistance to chemotherapeutics, in spite of clear evidence of metastasis. To motivate this choice of treatment a liquid biopsy for circulating tumor DNA (Heitzer et al., 2015) (released by dying malignant cells which have left the initial site of the neoplasm) is required – however, this method is not fully validated in the case of breast cancer. Furthermore, genetic testing of the extracted tumor, such as OncoType Dx (McVeigh et al., 2014), would also be required to establish the efficiency of chemotherapeutics.

Based on the age of onset and positive family history, a BRCA mutation was suspected. However, unveiling the mutation for CHEK2 opens a Pandora's box of potential malignancies to screen for. The extent of screening needed to cover both BRCA2 and CHEK2 associated cancers is impossible to apply in clinical practice. In this case, genetic testing gave us insight - however, this was at the cost of inducing anxiety in the patient.

Due to the presence of mutant pathogenic variants in the BRCA2 and CHEK2 genes, the patient needs to be informed about the increased risk of developing other forms of cancer – such as ovarian, pancreatic cancer and melanoma, in the case of BRCA2 (***, 1999), or colon (Cybulski et al., 2004) and thyroid cancer (Cybulski et al., 2004; Siołek et al., 2015), in the case of CHEK2. Prevention of these forms of cancer needs to be carried out as well, through early screening (where available). For ovarian cancer, which poses a high risk of developing in patients with a recent medical history of breast cancer and positive genetic testing (Siołek et al., 2015), prophylaxis can be performed through hormonal therapy - due to the presence of estrogen and progesterone receptors in the breast tissue, complete hysterectomy being a last-resort choice in the case of young women.

There is scarce information about the particular pathogenic variant of the CHEK2 gene (Cybulski et al., 2015) and the overall correlation of this gene's mutant forms with any particular form of cancer. Although this gene has been seen as an adjuvant gene in triggering the malignant growth, its sole potency is still unknown. Research has been conducted on restricted populations to show that CHEK2 pathogenic variants can induce a higher risk on their own (Cybulski et al., 2011), but their function is still unknown in the process of malignant development. Through further research, we could gain a better knowledge of this gene's particular role in the development of neoplasms, aiding

us in understanding this disease and in improving our prophylactic measures.

This case also brings awareness regarding hereditary male breast and prostate cancer. The patient's descendants have a high risk of developing these two forms (Siołek et al., 2015; Silvestri et al., 2016): this poses the problem of early screening – a domain that still needs research and the proposal of new techniques and markers, due to the controversial nature of current methods (such as PSA testing for prostate cancer) (Cuzick et al., 2014). The potential to transmit the mutation to descendants is another cause of distress in a patient diagnosed with a hereditary form of cancer.

While hereditary breast cancer only accounts for up to 10% of breast cancer cases, a screening program for it is a dire need for our society. A diagnosis of hereditary cancer brings a heavy emotional burden to the patient - accepting invasive treatment, accepting the possibility of a further cancer, as well as the potential to transmit any mutation to offspring. Although our first thought is to introduce genetic testing as a screening method for patients with positive family history, we cannot rule out *de novo* mutations that put at risk not only the patient, but also the next generations. This, alongside financial reasons, is why genetic testing may not surface as a mainstream screening technique for years to come - in spite of its dramatic effects on therapeutic management in selected cases.

Conclusions

1. The diagnosis of breast cancer in a relatively young patient with positive oncological family history brings forward the suspicion of hereditary cancer.

2. Once confirmed, a diagnosis of hereditary cancer has implications for the patients' treatment and prognosis, as well as screening relatives for carrier status.

Conflicts of interests

There are no conflicts of interests.

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