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BRIEF REPORT

Double heterozygous mutation in the BRCA1 and ATM genes involved in development of primary metachronous tumours: a case report

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Abstract

Purpose Between 5 and 10% of cases of breast cancer (BC) are attributable to a genetic susceptibility. The BRCA1 and BRCA2 genes described in the late 1990s are associated with an increased risk of breast and ovarian cancer, and the clinical management of carriers of pathogenic variants in these genes is defined in several clinical guidelines (Paluch-Shimon et al. in Ann Oncol 27(suppl 5):v103–v110, 2016; Llort et al. in Clin Transl Oncol 17(12):956–961, 2015). However, the pathogenic variants in BRCA1 and BRCA2 represent only a third of the causes of hereditary BC (Easton et al. in N Engl J Med 372:2243–2257, 2015). The incorporation of NGS (Next Generation Sequencing) techniques in the genetic diagnosis of this pathology, in addition to minimising the cost and time of analysis, allows the simultaneous study of other genes of high and moderate penetrance (Easton et al. in N Engl J Med 372:2243–2257, 2015; Op. Cit.; Tung et al. in Cancer 121(1):25–33, 2015). To date, there are not many cases or series of patients that describe the co-occurrence of two pathogenic variants in these genes of BC. Cases of double heterozygosis have been described with the presence of pathogenic variants in BRCA1, BRCA2, PALB2, CHEK2, BLM or NBN (Nomizu et al. in Breast Cancer 22(5):557–61, 2015; Heidemann et al. in Breast Cancer Res Treat 134(3):1229–1239, 2012; Zuradelli et al. in Breast Cancer Res Treat 124(1):251–258, 2010; Sokolenko et al. in Breast Cancer Res Treat 145(2):553–562, 2014).

Methods We report the case of a patient diagnosed with multiple tumours who presented two pathogenic variants in heterozygosis.

Results Two pathogenic variants, c.5123C > A (p.Ala1708Glu) in the BRCA1 gene and c.2413C > T (p.Arg805X) in the ATM gene were detected in heterozygosis. Said variants were confirmed by Sanger-type sequencing using specific primers.

Conclusions The implementation of gene panels using NGS in the study of hereditary cancer involves the detection of heterozygous double mutations in genes of high and moderate penetrance for cancer, although with a low frequency.

Keywords ATM · BRCA1 · Breast cancer · Double heterocygote

Case report

A woman with medical history of overweight, blood hypertension and bronchial asthma. In the year 2000, at the age of 55 years, she was diagnosed with triple-negative breast carcinoma. Unilateral radical mastectomy and axillary lymphadenectomy were performed. She received adjuvant anthracycline- and taxane-based chemotherapy and adjuvant radiotherapy (40 Gy).

In 2007, at the age of 62, she presented with jaundice and elevated transaminases and was diagnosed with an ampuloma pT2N0M0. Treatment was exclusively surgical, comprising a pancreaticoduodenectomy'. The histological type was a moderately differentiated infiltrating adenocarcinoma.

In 2016, at the age of 71 years, a high-grade stage IIIC clear-cell endometrial adenocarcinoma was diagnosed. A total hysterectomy and bilateral salpingo-oophorectomy were performed. A year later, she was diagnosed with lung metastases and died in September 2018.

The patient's family tree is shown in Fig. 1.

DNA was extracted from peripheral blood. The exonic and adjacent intronic regions and CNVs of the following 26 genes were analysed by NGS: BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, ATM,

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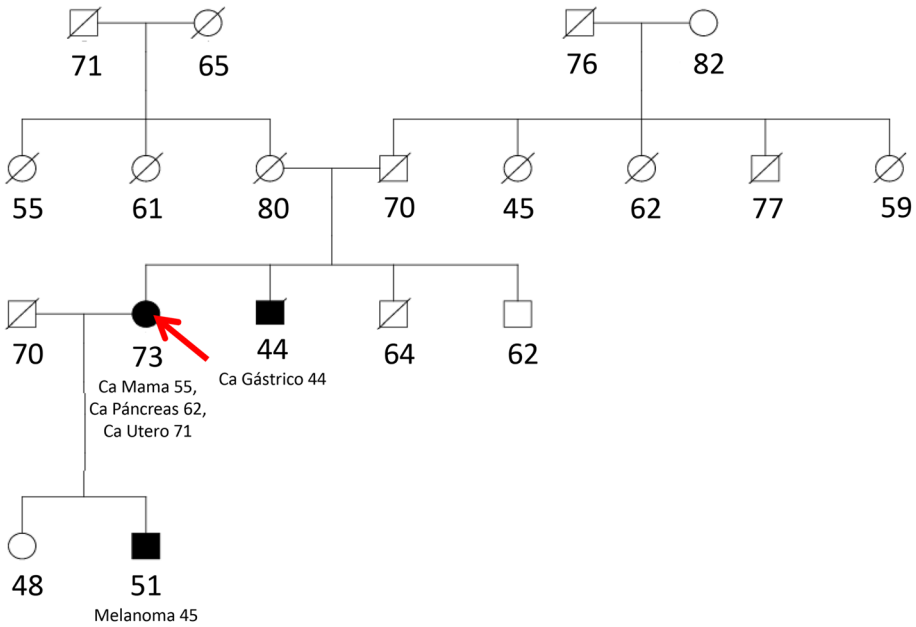

Fig. 1 Family tree

PALB2, CHEK2, BRIP1, RAD51C, RAD51D, TP53, PTEN, PIK3CA, STK11, CDH1, NBN, BARD1, RAD50, MRE11A, FAM175A and XRCC2.

Two pathogenic variants, c.5123C > A (p.Ala1708Glu) in the BRCA1 gene and c.2413C > T (p.Arg805X) in the ATM gene were detected in heterozygosis. Variant (p.Ala1708Glu) involves the alteration of a conserved nucleotide located in the BRCT domain of the protein, and in multiple studies it has been shown that in several families with breast and ovarian cancer, the variant cosegregates with the disease. Variant (p.Arg805X) generates a truncated protein and must also be considered as pathogenic. Said variants were confirmed by Sanger-type sequencing using specific primers (Fig. 2).

The direct study of both pathogenic variants in the patient´s children has been carried out. It has not been possible to carry out the study in other relatives because they

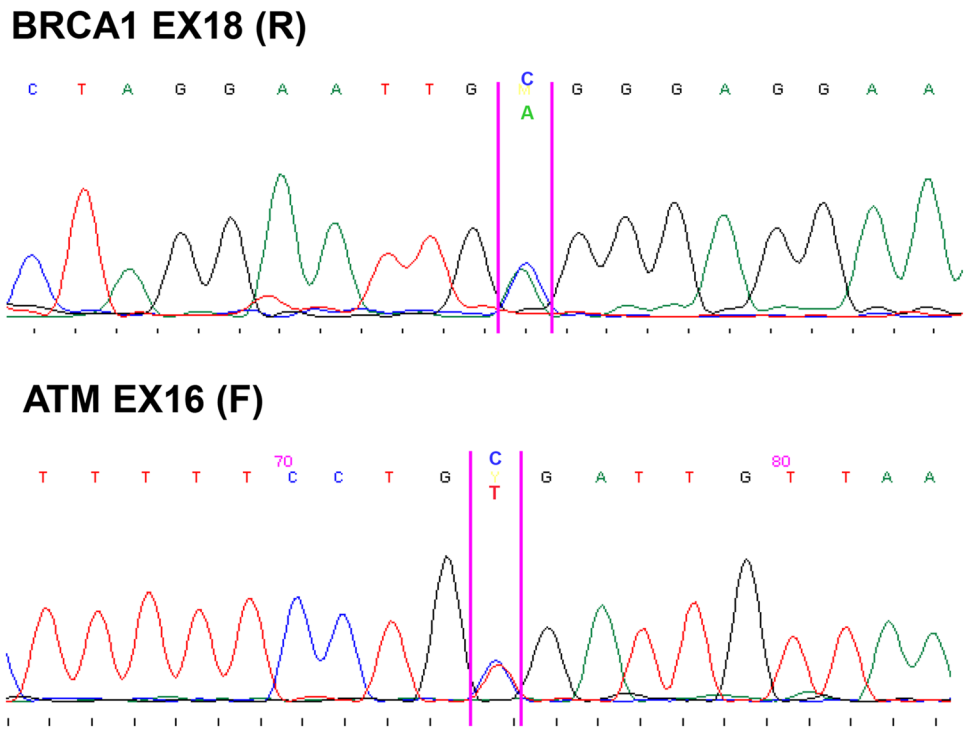

Fig. 2 Sanger-type sequencing genomic DNA of the patient. The nucleotide change is marked in red. **a** Sequencing of exon 18 of the BRCA1 gene where the c.5123C > A mutation is detected in heterozygosis and **b** sequencing of exon 16 of the ATM gene where it detects the c.2413 C > T mutation in heterozygosis

have died or the patient did not have contact with them. Her son is a carrier of the two variants while her daughter is a carrier of the ATM variant only.

The pathogenic variant in the ATM gene confers a moderate risk of BC (increased risk of 2–4 times). The daughter of 48 years is a carrier of this variant and was recommended annual mammographic screening.

The 51-year-old son, diagnosed with skin melanoma at 45 years of age and double heterozygote of the two variants, was recommended for screening as a male carrier of a pathogenic variant in BRCA1.

Discussion

Mutation carriers in BRCA1 have a high risk of breast and ovarian cancer. According to data from a prospective cohort of carriers, the cumulative risk to 80 years of BC is 72% (95% CI 65–79%) and ovarian cancer is 44% (95% CI 36–53%) [9]. BCs associated with mutations in BRCA1 exhibit a triple-negative phenotype more frequently, and the age of presentation is earlier [10, 11]. Regarding the risk of suffering from other breast and ovarian tumours for BRCA1, it has not been clearly established [12], although a higher incidence of melanoma has been reported in a population study.

The ATM protein is a protein kinase that phosphorylates different tumour suppressor proteins, among which is the BRCA1 protein [13]. Homozygous or double heterozygous mutation of the ATM gene causes the human disease ataxia-telangiectasia (AT), a disease characterised by progressive cerebellar ataxia. In contrast, mutations in heterozygosis have been associated with a moderate risk of BC [14].

The coexistence of mutations in BRCA1 and ATM has been previously studied, although not very widely, both in vitro and in the murine model. Mouse studies demonstrated that heterozygous mutations in ATM in knock-out mice deficient in BRCA1 increase the severity of mammary gland cancer and reduce ductal branching, suggesting a synergistic interaction in tumorigenesis when both proteins are depleted [15]. Subsequent in vitro studies indicate that double heterozygosity for ATM and BRCA1 leads to a higher cell transformation rate than does single heterozygosity [16]. They demonstrated that delayed recognition of DNA damage, disturbed cell cycle checkpoint, incomplete DNA repair and increased genomic instability were involved in the biological networks [17].

So far, only two cases of double heterozygosis in ATM and BRCA1 have been reported: in two patients with BC presented at an early age and who had the p.C61G mutation in the BRCA1 gene and the p.E1978X mutation in the ATM gene. BC in both cases had no expression of oestrogen receptors [18], similar to the case we report.

There are other combinations of heterozygous double mutations in BRCA and other genes of moderate penetrance, such as PALB2 and CHEK2, and dual heterozygous patients for BRCA1 and BRCA2 have also been described [19]. It could be expected that the severity of the pathology in double versus simple heterozygotes would be greater, with an earlier disease debut, and/or a greater number of tumours. Some case series of double heterozygotes of BRCA1 and BRCA2 report a diagnosis of earlier disease and higher frequency of multiple primary tumours [19]. However, the involvement of other genes such as ATM does not seem to increase the severity of the phenotype [18], although there are not enough cases reported. In our case, the onset age was not early, but there were a high number of primary carcinomas (breast, pancreas and uterus).

Traditionally, genetic counselling in hereditary cancer was associated with the discovery of mutations in a specific gene (BRCA1, BRCA2, MLH1, MSH2, MSH6, APC…). The implementation of gene panels using NGS in the study of hereditary cancer involves the detection of heterozygous double mutations in genes of high and moderate penetrance for cancer, although with a low frequency. In this paper, we present a case of a double heterozygote in BRCA1 and ATM that has been diagnosed with three primary metachronous tumours.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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