





Pathogenic variants in *BRCA1/2* genes among patients with triple-negative breast cancer: a case series

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ABSTRACT

Triple-negative breast cancer (TNBC) is an uncommon molecular subtype (representing 15%–20% of breast cancers) characterized by the non-expression of estrogen receptor, progesterone receptor, and human epidermal growth receptor factor 2. More aggressive and lethal, TNBC is often associated with pathogenic variants in *BRCA1/2* genes. This study aimed to describe a series of seven cases of patients with TNBC and pathogenic variants in *BRCA1/2* genes. All patients were female and under 50 years of age at diagnosis. Four of them presented a family history of breast cancer and/or other neoplasms. The predominant clinical stage was IIB, and the main anatomopathological stage was pT2pN0M0. The mean tumor size in the series was 2.5 cm (1.0 to 3.2 cm). Ki-67 was > 30% in all patients. Three cases (43%) had pathological complete response, and only one presented extensive residual disease after neoadjuvant chemotherapy. Six patients showed pathogenic variants in *BRCA1* (86%) and one in *BRCA2+* (14%). After a mean follow-up of 38 months (19 to 68 months), five patients were alive and without neoplastic disease, and two progressed to metastasis.

KEYWORDS: mutation; genes, *BRCA1*; genes, *BRCA2*; triple negative breast neoplasms; case reports.

INTRODUCTION

Triple-negative breast cancer (TNBC) is a molecular subtype characterized by the non-expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor factor 2 (HER2). With a worse prognosis and lower survival, TNBC represents 15% to 20% of breast cancers and is more frequent in black and Hispanic women^{1,2}.

TNBC is also associated with a higher incidence of pathogenic variants in *BRCA1/2* genes, especially in *BRCA1*³. Study conducted by Barreta et al. showed that the overall survival (OS) of patients with no pathogenic variants in *BRCA1/2* is greater than among *BRCA1/2+* patients. However, recurrence-free survival (RFS) presented no significant difference⁴.

Identifying patients with TNBC and *BRCA1/2* pathogenic variants is important because it allows defining risk-reducing surgical strategies (contralateral mastectomy and bilateral salpingo-oophorectomy) and administering systemic treatments (use of platinum agents in neoadjuvant therapies and poly [ADP-ribose] polymerase inhibitors — PARP [Olaparib] in metastatic settings)^{5,6}.

This study aimed to describe a series of seven cases of patients with TNBC and pathogenic variants in *BRCA1/2* genes.

CASE SERIES

As shown in Table 1, all patients were female. The mean age in the series was 37 years (28 to 48). Six patients (86%) had pathogenic variants in *BRCA1* and one (14%) in *BRCA2+*. The mean tumor size was 2.5 cm (1.0 to 3.2 cm). Five patients (71%) presented clinical stage IIB and anatomopathological stage pT2pN0M0. All of them received surgical treatment, neoadjuvant chemotherapy, and adjuvant radiotherapy. After a mean follow-up of 38 months (19 to 68 months), all patients were alive, but two presented metastatic neoplastic disease (case 5 since March 2020 and case 6 since February 2020).

Case 1 patient reported an extensive family history of breast cancer: four maternal cousins (one deceased), one paternal cousin, and a sister (diagnosed with breast cancer at 44 years of age). In addition, she had a maternal aunt with ovarian cancer (death at 74 years) and two paternal uncles with lung cancer. Case 3 patient declared as family history of cancer: her mother (diagnosed with breast cancer at 30 years of age in the 1980s, dying at the age of 36), father (lung cancer), paternal grandmother (pancreatic cancer), a maternal cousin (ovarian cancer), and a paternal aunt and paternal cousin (hematological neoplasms). Case 4 patient also

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had a family history of cancer: her father, who died as a result of prostate cancer, and a maternal aunt, who had cervical cancer. Case 5 patient did not know her family history because she

is adopted and has no contact with her biological family. Case 7 patient stated that her mother was diagnosed with breast cancer at 35 years of age and died at 45.

Table 1. Description of variables associated with patients in the series.

Description	Patients	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gender		Female	Female	Female	Female	Female	Female	Female
Age at diagnosis (years)		38	36	47	48	28	32	32
Previous pregnancies (number)		4	0	1	5	1	3	0
Comorbidities		None	None	None	None	None	None	None
Family history of breast cancer		Yes	No	Yes	No	Unknown	No	Yes
Family history of other neoplasms		Yes	No	Yes	Yes	Unknown	No	No
Histological type		NST	NST	NST	NST	NST	NST	NST
Tumor size (cm)		2.5	2.3	1.0	2.8	3.2	2.8	2.9
Cell differentiation grade		G3	G2	G2	G3	G3	G2	G2
Angiolymphatic invasion		No	No	No	No	No	Yes	No
Perineural invasion		No	No	No	No	No	No	No
Ki-67 (%)		60	40	40	70	90	80	40
Molecular subtype		TN	TN	TN	TN	TN	TN	TN
Axillary involvement (number of lymph nodes)		No	No	No	No	Yes (4)	No	No
Metastasis at diagnosis		No	No	No	No	No	No	No
Clinical stage		IIB	IIB	IB	IIB	IIIC	IIB	IIB
Anatomopathological stage		pT2pN0M0	pT2pN0M0	pT1pN0M0	pT2pN0M0	pT2pN2M0	pT2pN0M0	pT2pN0M0
Surgical treatment		M+SLN+AD	M+SLN	M+SLN	SR+SLN	M+SLN+AD	SR+SLN	M+SLN
Contralateral mastectomy		Yes	Yes	Yes	No	Yes	No	Yes
Salpingo-oophorectomy		No	No	Yes	Yes	No	Yes	No
Complementary treatment		NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART
Immunotherapy		No	No	No	No	No	No	No
Olaparib		No	No	No	No	Yes	Yes	No
Sentinel lymph node		Negative	Negative	Negative	Negative	Positive	Negative	Negative
Pathological response		pCR	pCR	RCB-II	RCB-I	RCB-III	RCB-II	pCR
Pathogenic mutations (<i>BRCA1/2</i>)		<i>BRCA1</i>	<i>BRCA1</i>	<i>BRCA1</i>	<i>BRCA2</i>	<i>BRCA1</i>	<i>BRCA1</i>	<i>BRCA1</i>
Clinical course		ADF	ADF	ADF	ADF	Metastasis	Metastasis	ADF

NST: invasive carcinoma of no special type; TN: triple-negative; M: mastectomy; SR: segmental resection; SLN: sentinel lymph node; AD: axillary drainage; NACT: neoadjuvant chemotherapy; ART: adjuvant radiotherapy; pCR: pathological complete response; RCB-I: minimal residual cancer burden; RCB-II: moderate residual cancer burden; RCB-III: extensive residual cancer burden; ADF: alive and disease-free.

Table 2. Description of *BRCA1/2* pathogenic variants detected in the patients in the series.

Patient	Gene	Pathogenic variant (allele profile)	Protein	Molecular consequence	Accession number in ClinVar
Case 1	<i>BRCA1</i>	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14
Case 2	<i>BRCA1</i>	c.5266dupC (heterozygosity)	p.Gln1756fs	*	VCV000017677.29
Case 3	<i>BRCA1</i>	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14
Case 4	<i>BRCA2</i>	c.2167delA (heterozygosity)	*	*	New (not described in ClinVar)
Case 5	<i>BRCA1</i>	c.4675+1G>A (heterozygosity)	*	Splice donor	VCV000055256.15
Case 6	<i>BRCA1</i>	c.655G>A (heterozygosity)	p.Asp219Asn	Missense	VCV000055655.7
Case 7	<i>BRCA1</i>	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14

*No associated data in ClinVar (<https://ncbi.nlm.nih.gov/clinvar/>).

Table 2 shows the *BRCA1/2* pathogenic variants found. Among the *BRCA1* pathogenic variants, three corresponded to the identical frameshift type (c.3331_3334del [p.Gln1111fs] in heterozygosity, determining a truncated protein), and these probands were not from related families.

This case series originated from a study based on medical records of patients diagnosed with breast cancer, part of a scientific project approved by the Research Ethics Committee (REC) of the Universidade Estadual do Piauí, Teresina (Piauí), Brazil, under the Certificate of Presentation for Ethical Consideration (*Certificado de Apresentação para Apreciação Ética* — CAAE) No. 30154720.0.0000.5209. All Brazilian ethical directives on research were observed (National Health Council Resolution No. 466/12).

DISCUSSION

In this study, all patients were under 50 years of age at diagnosis. Robertson et al. performed the genetic analysis of 308 patients with TNBC and found 45 cases with *BRCA1* pathogenic variants. They concluded that the chances of patients with TN tumors having *BRCA1* pathogenic variants are higher before the age of 50 years (above 10%). This finding justifies the National Comprehensive Cancer Network (NCCN) recommendation to test all patients diagnosed with TNBC before the age of 60 for *BRCA1/2*⁹.

Among the six patients who knew their family history, four presented a family history of breast cancer and/or other neoplasms. Family history is a known risk factor for the development of breast cancer, with higher frequency in patients with *BRCA1/2* pathogenic variants, which also occurred in this study¹⁰.

After univariate and multivariate analyses, Lopes et al. showed that angiolymphatic invasion and larger tumor size were factors associated with worse prognosis in TNBC¹¹. In this series, the two cases that progressed to metastasis presented tumor sizes larger than the mean of the series (2.5 cm), and case 6, who progressed to metastasis, showed angiolymphatic invasion.

Ki-67 is an important prognostic factor related to worse TNBC progression¹². However, greater knowledge about its cut-off point is needed, with some studies indicating a value of approximately 30%^{13,14}. In this series, all patients had Ki-67 values >30%.

Silva et al. revealed that TNBC is a predictive factor for pathological complete response (pCR), occurring in about 40% of these patients¹⁵. Other studies also associate TN tumors in patients with *BRCA1/2* pathogenic variants with higher chemoresponsiveness^{16,17}. In this study, three patients (43%) had pCR, and only one presented extensive residual disease (residual cancer burden — RCB-III) after neoadjuvant chemotherapy, ratifying literature data.

Six patients showed pathogenic variants in *BRCA1* and one in *BRCA2*. The literature also indicates a higher prevalence of *BRCA1* in young women diagnosed with TNBC compared to *BRCA2*^{18,19}. Case 4 presented the novel pathogenic variant c.2167delA in *BRCA2* (not yet described in ClinVar). Nonetheless, this variant has been described in the literature. In the study by Palmero et al. on *BRCA1/2* pathogenic variants in 649 probands of 28 centers from 11 Brazilian states, the authors analyzed 208 *BRCA2*+ probands and also found the pathogenic variant c.2167delA in one of them²⁰.

Literature data indicate that patients with *BRCA1* and *BRCA2* pathogenic variants have a 27% and 19% probability of developing contralateral breast cancer after primary tumor surgery in the ipsilateral breast, while this risk is only 5% in the general population. At the same time, contralateral mastectomy shows no benefits regarding OS in these patients. In turn, bilateral salpingo-oophorectomy reduces the risk of cancer recurrence in the ipsilateral and contralateral breast in *BRCA1/2*+ patients, improving their OS. Bilateral salpingo-oophorectomy also decreases the likelihood of ovarian cancer by more than 80% in *BRCA1/2*+ patients²¹. In addition, risk-reducing surgical strategies are more beneficial to younger patients with TNBC and *BRCA1/2*+ and with pCR after neoadjuvant chemotherapy⁵. In this study, all patients underwent risk-reducing contralateral mastectomy and/or bilateral salpingo-oophorectomy.

After a mean follow-up of 38 months (19 to 68 months), five patients were alive and disease-free, while two progressed to metastasis before five years from diagnosis. The literature associates TNBC with worse clinical course and lower survival. However, immunotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors have also improved the prognosis of patients with TN tumors and *BRCA1/2* pathogenic variants^{22,23}. In this series, case 5 developed metastasis to lymph nodes, lungs, adrenal glands, and bones 20 months after the initial diagnosis, and case 6 developed metastasis to lymph nodes and the central nervous system 41 months after the initial diagnosis. Olaparib (a PARP inhibitor) was administered as a therapeutic option for these two patients after metastasis. Both patients (cases 5 and 6) are still alive and on clinical follow-up 9 and 10 months after systemic recurrence, respectively.

The limitations of this study include the sample size and being performed in a single oncology center.

CONCLUSION

Among the seven patients with TNBC and *BRCA1/2* pathogenic variants in this series (all women, with a mean age of 37 years and mean tumor size of 2.5 cm), three (43%) presented pCR, and only one had RCB-III after neoadjuvant chemotherapy. The mean follow-up time was 38 months. At the end of follow-up, all patients were alive, and two presented systemic neoplastic disease before five years from diagnosis.

AUTHORS' CONTRIBUTIONS

R.E.A.R.C.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — original draft, Writing — review & editing.

F.T.R.O.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — original draft.

A.L.N.A.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — review & editing.

S.C.V.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — review & editing.

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