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Original research article

Significance of BRCA1 expression in breast and ovarian cancer patients with brain metastasis – A multicentre study

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ABSTRACT

Purpose: Cerebral metastases develop in 10–30% of patients with breast cancer (BC) and in around 3.3 to 4% of patients with ovarian cancer (OC). The aim of the multicenter study is to investigate the correlation between the expression of estrogen alpha receptors (ERα), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), stromal cell-derived factor 1 (SDF1) and its receptor C-X-C chemokine receptor type 4 (CXCR4), breast cancer metastasis suppressor 1 (BRMS1), astrocyte elevated gene 1 (AEG1), depending on the status of BRCA1 protein, in patients suffering from OC and BC with brain metastases.

Patients and methods: The analysis included 51 patients: 29 with BC and 22 with OC, in whom brain metastases were disclosed.

Results: In most patients (65.5% of BC patients and 68.2% of patients with OC tumors) BRCA1 protein loss was found. No correlation was disclosed between the levels of ERα, PR receptors, HER2, SDF1, CXCR4, AEG1, BRMS1 and BRCA1 status, patient age, stage of disease advancement, grade of histological maturity of the cells, presence of metastases to lymph nodes. A statistically significant correlation was disclosed between the negative expression of PR receptors and a high expression of CXCR4 in patients with BC. High values of the AEG1 protein (linked to metastases) were detected alongside a high expression of BRMS1 (a suppressor of metastases).

Conclusions: Patients with BC and OC and brain metastases have a frequent loss of BRCA1 expression. The role of ERα, PR, HER2, SDF1, CXCR4, AEG1, BRMS1 in metastatic process needs further studies.

1. Introduction

Metastases to the brain develop in 9%–17% of adult patients with cancer. In recent decades an increased incidence of brain metastases has been observed, which may be linked to the application of new imaging techniques and efficacy of life-prolonging systemic treatment. Most

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frequently, brain metastases develop in the course of pulmonary and breast cancer and in melanoma. These three tumors are responsible for 67%–80% of all brain metastases [1–3].

In gynecological tumors, breast and ovarian cancers, brain metastases were found to be more frequent in women carrying *BRCA* mutations than in sporadic cancer. In breast cancer, such metastases were found to be associated with the expression of hormone receptors and human epidermal growth factor receptor 2 (HER2), as well as with the type of therapy applied [4–8]. The effects of the expression of various genes linked to brain metastases of breast and ovarian cancer has been discussed in a small number of papers [9–12].

1.1. Breast cancer

According to numerous data, the number of brain metastases of breast cancer, is increasing [8,13,14]. The review by Nayak et al. [1] reports that brain metastases of breast cancer develop in 10%–30% patients. They are more common in younger women and are linked to the histological type of cancer, ER (estrogen receptor) and PR (progesterone receptor) status, and HER2 expression [14–16]. In studies of 140 patients with breast cancer and a brain metastasis in the Anderson Cancer Center, as many as 91% of patients manifested ductal cancer. Additionally, in most patients, histological malignancy of G3 was disclosed and metastases to lymph nodes were identified. The majority did not carry any estrogen or progesterone receptors, overexpression of HER2 was detected in almost 50%. Triple negative cancer (TN) was diagnosed in 28% of the women [14].

Hayashi et al. [16] studied receptors in women originating from 24 oncological centers in Japan and concluded that 60% carried no receptors for estrogens but were positive for HER2 (ER-/HER2 +). Similar data on receptors in women with breast cancer who developed metastases have been presented by other authors [13,14]. Niikura et al. [17] examined HER2 status and found inconsistent expression in primary and metastatic tumors in the brain; the absence of HER2 expression might be linked to poorer patient survival. The studies also demonstrated that treatment with trastuzumab increased the frequency of brain metastases [1,7,8].

1.2. Ovarian cancer

Brain metastases of ovarian cancer are not common: they manifest in around 3.3–4% of patients [18,19]. Studies in two oncological centers in Indianapolis (USA) showed that brain metastases developed in patients who were histologically proven to be carrying serous cancers (serous adenocarcinoma), manifesting a histological differentiation of G2 and G3 and in the III and IV stage of clinical advancement [19].

In our earlier study, brain metastases of ovarian cancer also developed in patients in stage IC according to FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) [20]. Other studies on HER2 expression showed that its overexpression may lead to metastases in the ovarian cancer cases [21]. Subsequent studies by Jernigan et al. [4] showed that of the women tested genetically with brain metastases over 70% carried *BRCA1* mutations. Nevertheless, the authors thought that the association with metastases remained hypothetical and required further investigation. According to Albiges et al. [6] and Sekine et al. [22] brain metastases in women with *BRCA1* mutations are frequent.

Apart from those already described, numerous factors affect the development of metastases of breast and ovarian cancers: the suppressor function of the ER β and *BRMS1* (breast cancer metastasis suppressor 1) was described as well as the effects of other genes linked to metastases, such as *SDF1/CXCR4* (stromal cell-derived factor-1/C-X-C chemokine receptor type 4) and AEG1 (astrocyte elevated gene) [10,11,23–27].

The study aimed to examine the correlation between:

Table 1
Characteristics of patients included in the study.

	Histological type of cancer	Clinical advancement stage	Grading
Breast cancer patients			
1	Ductal	T1c N0 M0	G3
2	Ductal	T1c N0 M0	G2
3	Ductal	T1 N0 M0	G3
4	Ductal	T1c N1mic M0	G2
5	Ductal	T1 N1 M0	G3
6	Ductal	T1c N1 Mx	G3
7	Ductal	T1c N1a Mx	G3
8	Ductal	T1b N2a M0	G2
9	Ductal	T2 N0 M0	G3
10	Ductal	T2 N1 M0	G2
11	Ductal	T2 N1a M0	G3
12	Ductal	T2 N1 M0	G3
13	Ductal	cT2b N1 M0	X
14	Ductal	T2 N2 M0	G2
15	Ductal	T2 N2 Mx	G2
16	Ductal	T2 N2 Mx	G3
17	Ductal	T2 N2 M0	X
18	Ductal	T3 N1 M0	X
19	Ductal	T3 N2 M0	G3
20	Ductal	T3 N2 M1	G2
21	Ductal	T4 N1b M0	G2
22	Ductal	T4 N1 M1	X
23	Ductal	T4b N1a Mx	G3
24	Ductal	T4 N2 M0	G2
25	Ductal	T4d N2a M0	G2
26	Ductal	T4 N2 M1	G3
27	Ductal	T4c N2 M1	G2
28	Ductal	TxN0M1	X
29	Lobular	pT2pN1Mx	G2
Ovarian cancer patients			
1	Serous	II	High
2	Serous	IIIC	High
3	Serous	IIIC	High
4	Serous	IIIC	High
5	Serous	IIIC	High
6	Serous	IIIC	High
7	Serous	IIIC	High
8	Serous	IIIC	High
9	Serous	IIIC	High
10	Serous	IV	High
11	Serous	IV	High
12	Serous	No staging	High
13	Serous, partially clear cell	I	High
14	Serous, partially clear cell	IIIC	High
15	Serous, partially endometrioid	IIIC	High
16	Serous, partially endometrioid	IV	High
17	Clear cell	IC	High
18	Endometrioid	IIB	High
19	Endometrioid	IV	High
20	Mucous	IIIC	High
21	Hypercalcemic, small cell	IV	High
22	Undifferentiated	IIB	High

- clinical-pathological factors (patient age, histological type of cancer, stage of clinical advancement, grade of histological maturity – grading (G),
- status of ERα, PR, HER2 receptors (in cases of breast cancer), ER α (in cases of ovarian cancer)
- molecular factors linked to metastases: SDF1, CXCR4, AEG1, BRMS1 in women with brain metastases, depending on the expression of BRCA1 in tissues of primary tumors

2. Material and methods

2.1. Study population

In our multicenter study, we included 51 patients: 29 with breast cancer and present brain metastases, and 22 with ovarian cancer and

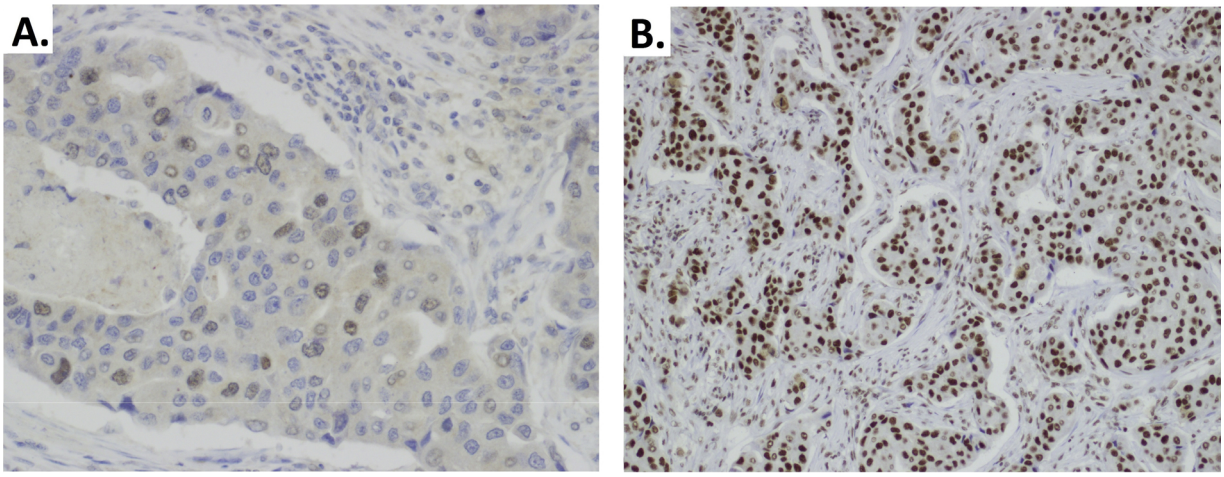

Fig. 1. Positive immunohistochemical staining of a) BRCA1 and b) BRMS1.

present brain metastases (Table 1). The mean age of patients upon diagnosis of the disease in the group of women with breast cancer amounted to 54.6 years and 53.1 years in the group of patients with ovarian cancer.

Twenty-eight patients with breast cancer had been diagnosed with ductal cancer, one patient had lobular cancer. Among patients with ovarian cancer, 12 patients had serous tumor, 4 of partially serous histology and the remaining were diagnosed with endometrioid, clear cell, low differentiated, hypercalcemic or mixed histology.

2.2. Immunohistochemistry - method

The histopathological samples used in the study were archive paraffin blocks with the cancer tissue from the primary surgery for ovarian or breast cancer. The tissue material was fixed in 10% buffered formalin, pH 7.4, and placed in a processor. The tissue was paraffin-embedded at a temperature of 60 °C using standard histopathological methods. The appropriately marked paraffin blocks obtained in this way were cut in a microtome into 4–5 μm thick sections, placed on adhesive microscope slides and left for 1 h at a temperature of 60 °C. Antibodies were used (Roche Diagnostics, Switzerland) to estimate HER2, anti-HER2/neu (clone 4B5). Samples with score 2+ according to ASCO/CAP criteria were examined by FISH method described in ASCO/CAP guidelines [28]. The immunohistochemical method was applied using the ultraView Universal DAB Detection Kit (Roche Diagnostics, Switzerland). Immunoperoxidase staining was conducted in BenchMark Ultra apparatus (Ventana Medical System/Roche Diagnostics, Switzerland). The studies took advantage of the immunohistochemical technique using DAKO En Vision™FLEX + System (DAKO, Denmark). In the paraffin sections antigens were uncovered in Target Retrieval Solution, High pH (DAKO, Denmark) in PT-link apparatus, at a temperature of 97 °C, for 20 min. Estrogen alpha and progesterone receptors were estimated using DAKO monoclonal antibodies (DAKO, Denmark). The markers were detected using RTU: ER antibodies, clone EP1, PR clone 636, using an immunohistochemical technique with the DAKO En Vision™ Flex System. Immunoperoxidase staining was conducted in the Autostainer Link 48 apparatus (DAKO, Denmark). Monoclonal and polyclonal antibodies were employed (Abcam, UK) to estimate SDF1, AEG1, CXCR4, BRMS1 markers as well as BRCA1. In staining, primary antibodies: anti-SDF1 ab 18,919 (dilution 1:500), Anti-AEG1 [EP4445] ab 124,789 (dilution 1:250), anti-CXCR4 [UMB2] ab 124,824 (dilution 1:500), anti-BRMS1 [EPR 7202] ab134968 (dilution 1:500) and anti-BRCA1 [MS110] ab 16,780 (dilution 1:200) were used. Subsequently, the DAKO EnVision™FLEX/HRP (DAKO, Denmark) was used with an incubation time of 20 min. In turn, the sections were incubated with the En Vision™ FLEX DAB + Chromogen (DAKO, Denmark) for 5 min. The immunoperoxidase staining was conducted manually, at room temperature. Estrogen receptors β were estimated using the polyclonal antibody (Biogenex, US), diluted 1:500. In the paraffin sections, the antigens were retrieved using the Target Retrieval Solution, low pH (DAKO, Denmark), in PT-link apparatus at a temperature of 97 °C, for 20 min. The DAKO En Vision™ FLEX/HRP system was used, incubation time: 20 min. The sections were then incubated in En Vision™FLEX DAB + Chromogen for 5 min. Immunoperoxidase staining was conducted manually at room temperature.

2.3. Immunohistochemistry - assessment

The immunohistopathological reaction in each cancerous tumor sample was assessed, depending on the intensity, as a positive or negative. Positive reaction was assessed when positive staining was detected in more than 10% of cancer cells. Lack of protein expression or positive immunohistopathological staining in less than 10% of cancer cells was found as negative reaction. HER2 scoring was interpreted according to ASCO/CAP criteria [28].

2.4. Statistical analysis

Statistical analysis was performed with Statistica 10 software (StatSoft Inc, USA). The Mann-Whitney, Kruskal-Wallis tests and Spearman's were used. Statistical significance was accepted at $p < 0.05$.

2.5. Ethics approval

This study was approved by the Bioethics Committee at Poznan University of Medical Science, Poland (approval number #KB 1052/18). This study was performed in compliance with the Declaration of Helsinki.

3. Results

BRCA1, BRMS1, ERα, PR immunohistochemical staining have shown nuclear pattern (Figs. 1 and 2). CXCR4 and HER2 reaction presented membranous type, while AEG1 and SDF1 staining was of a membrane and cytoplasmic type (Figs. 3 and 4).

3.1. Breast cancer patients

In 19 out of 29 (65.5%) patients with breast cancer, loss of BRCA1 expression was detected in the tumor tissue. No correlation could be detected between the expression of BRCA1 and the stage of disease

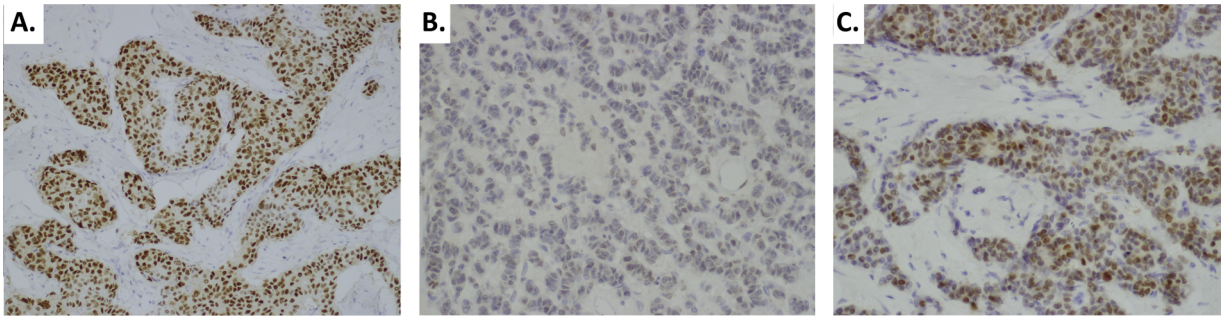

Fig. 2. Positive immunohistochemical staining of a) ER alfa; b) ER beta and C) PR.

advancement, histological maturity of cells, presence of metastases in axillar lymph nodes or of distant metastases ($p > 0.05$). A high expression of BRMS1 protein in tumor tissue was evident in all the patients while the expression of AEG1 protein was detected in all patients with ductal cancer but not in the patient with lobular breast cancer. Among the 29 patients, a high expression of ER receptors was detected in 11 patients (37.9%), and of progesterone receptors in 10 patients (34.5%) (Table 2). In 8 patients (27.6%) the presence of HER2 protein was detected using immunohistochemical techniques and amplification of the protein was confirmed using the FISH method. A high expression of SDF1 was evident in only 2 patients (6.9%) and high CXCR4 expression was noted in 11 patients (37.9%). In patients with breast cancer no significant differences were disclosed in the levels of ERα, PR, HER2, SDF1, CXCR4, BRMS1, AEG1 protein expression in the tumor cells ($p > 0.05$). Also, expression of the proteins manifested no correlation with patient age, stage of disease advancement, grade of histological maturity of the cells, presence of metastases to lymph nodes, presence of distant metastases. Women with a negative status of PR receptors manifested a high expression of CXCR4 ($p = 0.0436$) significantly more frequently. No other significant correlations was detected between the studied proteins.

3.2. Ovarian cancer patients

In the studied group of patients with ovarian cancer, a loss of BRCA1 expression in the tumor was detected in 15 out of 22 patients (68.2%). No correlation was disclosed between the level of BRCA1 expression and the grade of disease advancement, histological maturity of cells or age of the patients ($p > 0.05$). A high expression of BRMS1 protein in tumor tissue was recorded in 21 out of 22 patients (95.5%), while AEG1 protein expression was detected in 19 patients (86.4%) (Table 2). In 8 patients (36.4%) a high expression of ERα receptors was demonstrated. Similar to breast cancer, neoplastic cells of ovarian cancer in most cases (21 of 22 cases, 95.5%) did not manifest a positive reaction of SDF1 protein. Positive immunohistochemical reaction for CXCR4 receptor was detected in 12 cases (54.5%). In the group of patients with ovarian cancer, no significant differences were disclosed in the levels of expression of ERα, SDF1, CXCR4, BRMS1, AEG proteins which would depend on status of BRCA1 protein in neoplastic cells ($p > 0.05$). Also, no correlation was disclosed between the expression of the proteins and patient age, stage of advancement of the disease or histological type of the tumor.

4. Discussion

Brain metastases in the course of breast cancer develop in as many as 30% of patients [1,5]. Few studies have evaluated the effect of *BRCA* mutations on the frequency of their manifestation, despite the suspicion that brain metastases are thought to develop more frequently in these patients than in sporadic breast cancer [4,6,22]. In the study by Albiges et al. [6] as many as 67% of patients (10 women out of 15 patients) with breast cancer with the *BRCA1* mutation developed such metastases. No such metastases in patients with the *BRCA2* mutation was noted. However, the studies did not examine molecular variables which could affect the frequency of metastases.

BRMS1, the gene inhibiting metastases, is located on chromosome 11q13.1 – q13.2. The suppressor function was demonstrated to inhibit the nuclear signaling pathway (Nκ-kB) and phosphoinositide signaling. Moreover, it inhibits the expression of osteopontin (OPN) and urokinase plasminogen activator (uPAR) and reduces the adhesion of cells to components of the extracellular matrix. Its activity has been demonstrated in breast and ovarian cancers [9–11].

SDF1 involves a chemokine coded by the *SDF1* gene located on chromosome 10q11.1 [24]. It includes two forms: SDF1α and SDF1β, which differ in function. SDF1α represents a factor of chemotaxis, acting through the CXCR4 receptor present in neoplastic cells [25]. The

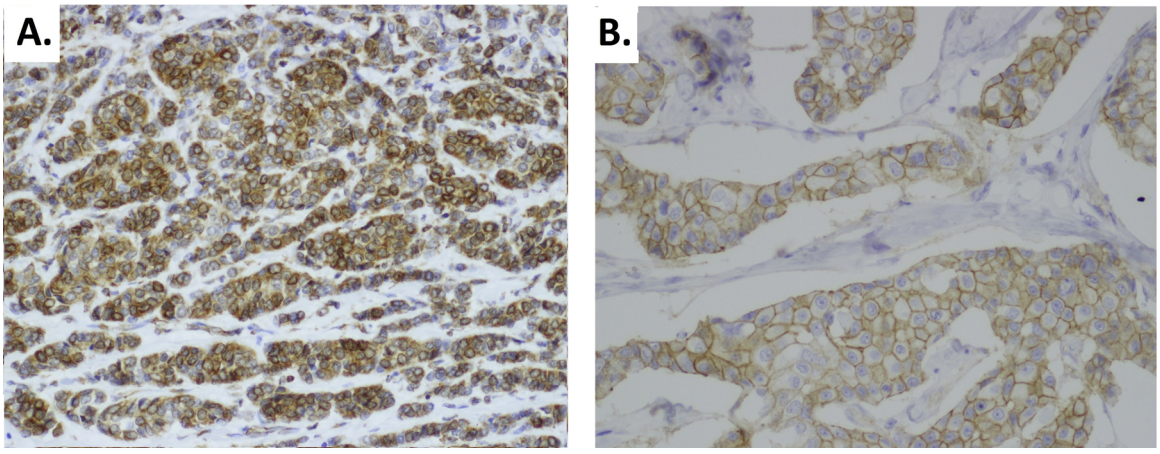

Fig. 3. Positive immunohistochemical staining of a) AEG1 and b) HER2.

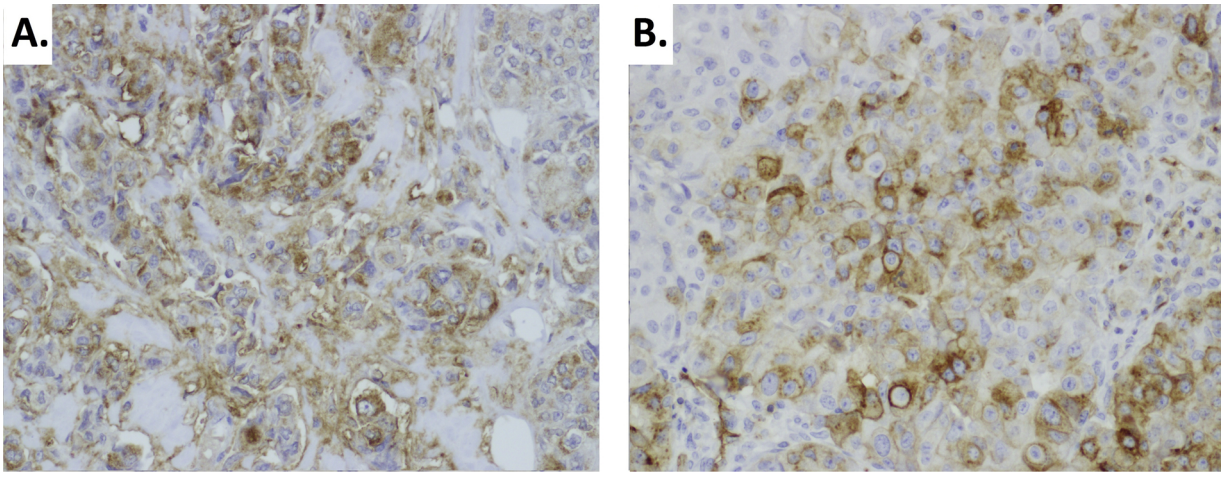

Fig. 4. Positive immunohistochemical staining of a) SDF1 and b) CXCR4.

Table 2
Positive immunohistochemical staining of selected proteins depending on the level of BRCA1 expression in neoplastic tissue in patients with breast cancer and ovarian cancer.

Breast cancer patients			
	BRCA1 – positive expression n = 10	BRCA1 – negative expression n = 19	Total n = 29 (100%)
ER	4 (40%)	7 (36.8%)	11 (37.9%)
PR	3 (30%)	7 (36.8%)	10 (34.5%)
HER2	3 (30%)	5 (26.3%)	8 (27.6%)
SDF1	1 (10%)	1 (5.2%)	2 (6.9%)
CXCR4	2 (20%)	9 (47.3%)	11 (37.9%)
AEG1	10 (100%)	18 (94.7%)	28 (96.6%)
BRMS1	10 (100%)	19 (100%)	29 (100%)
Ovarian cancer patients			
	BRCA1 – positive expression n = 7	BRCA1 – negative expression n = 15	Total n = 22
ER	3 (42.9%)	5 (33.3%)	8 (36.4%)
SDF1	0 (0%)	1 (6.7%)	1 (4.5%)
CXCR4	3 (42.9%)	9 (60.0%)	12 (54.5%)
AEG1	6 (85.7%)	13 (86.6%)	19 (86.4%)
BRMS1	7 (100%)	14 (93.3%)	21 (95.5%)

interaction of SDF1 and CXCR4 in many types of cancer is significant in the development of metastases to several tissues; CXCR4+ cells are directed to organs with SDF1 expression. Moreover, the SDF1/CXCR4 complex stimulates proliferation of breast and ovarian cancer cells in a manner similar to that of estradiol [25,26].

Gene *AEG1,* located on chromosome 8q22 codes for the protein of metadherin. The overexpression of AEG1 metadherin is associated with tumor invasion through the activation of the PI3K-Akt pathway which is also involved in oncogenic signaling. PI3K-Akt influences the NFkB nuclear factor associated with metastases through its effect on proteins of cell adhesion and chemokines. AEG1 plays a role in the anchorage of cancer cells [27,29,30].

Our study disclosed the loss of BRCA1 expression in breast tumor in 65.5% women (19 out of 29 patients). Precise frequency of somatic mutations remains unknown in the available literature. Li et al. [31] detected in breast cancer patient population around 5.5% of germline mutation and additionally 3% of somatic mutations of *BRCA1/2* genes. We examined the relationship of such protein loss with clinical-pathological variables with the status of receptors (ERα, PR, HER2) and with molecular factors associated with metastases: SDF1, CXCR4, AEG1 and BRMS. No such relationship was identified. In women with a negative status of PR receptor expression, the expression of CXCR4, the receptor for SDF1 proved to be more frequent, which may indicate a relationship between the PR expression and metastases. In studies by other authors, the SDF1/CXCR4 complex was demonstrated to be of key importance for metastases of several tumors, including breast and ovarian cancer [25,26]. Unfortunately, we failed to examine cancerous tissues in the brain to confirm, possibly, an elevated expression of SDF1, the cytokine guiding the cancer-presenting cells with CXCR4 at this site. In all cases of breast cancer (100%) we detected the expression of BRMS1, a metastases-inhibiting gene protein, but in 96.6% of cases we detected the expression of AEG1. The protein of the gene is responsible for the development of metastases through several mechanisms, including the anchorage of metastatic cells, activity of matrix metalloproteinases as well as function of protein kinase C. Thus, the process of metastatic development is extremely complex [27,32,33].

Brain metastases in the course of ovarian cancer are rare, which has also been confirmed by the European MITO analysis [34]. From the literature, the percentage of germline mutations in *BRCA1* in a general population of ovarian cancer patients is 15%, and somatic mutations are detected in around 3% [35,36]. In our study, the loss of BRCA1 expression in cancer cells was manifested in 68.2% women (15 out of 22 patients). We did not identify any relationship between the studied variables and BRCA1 status. It is interesting that the expression of CXCR4 manifested in over 50% of cases (54.5%) and the expression of AEG1 in the majority (86.4%) of cases. Such a result in cases of brain metastases could be expected but the high expression of the inhibitory *BRMS1* gene (in 95.5% of cases) seemed inadequate in the situation of existing metastases. The *BRMS1* gene is linked to the inhibition of metastases [9–11]. According to Hurst et al. [37], the suppression of metastatic development most probably depends on the interaction of the gene with multiple molecular factors. These interesting studies require correlating estimations of molecular variables in tissues of primary and metastatic tumors in the brain, to identify the molecular factors decisive for metastases more accurately.

5. Conclusions

Patients with BC and OC and brain metastases have a frequent loss of BRCA1 expression. The role of ERα, PR, HER2, SDF1, CXCR4, AEG1, BRMS1 in metastatic process needs further studies.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

The authors have no funding to disclose.

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Statistical Analysis: Monika Szarszewska.

Data Interpretation: Monika Szarszewska.

Manuscript Preparation: Anna Marowska, Janina Markowska, Monika Szarszewska, Violetta Filas, Andrzej Marszałek.

Literature Search: Robert Jach, Anna Marowska, Janina Markowska.

Funds Collection: n/a.

References

[1] Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012;14(1):48–54.
[2] Ahluwalia MS, Vogelbaum MV, Chao ST, Mehta MM. Brain metastasis and treatment. F1000Prime Rep 2014;6:114. https://doi.org/10.12703/P6-114.
[3] Cagney DN, Am Martin, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases and diagnosis of systemic malignancy. A population-based study. Neuro Oncol 2017;19(11):1511–21.
[4] Jernigan AM, Mahdi H, Rose PG. Epithelial ovarian Cancer Metastatic to the central nervous system and a family history concerning for hereditary breast and ovarian Cancer-A potential relationship. Int J Gynecol Cancer 2015;25(7):1232–8.
[5] Zavitsanos PJ, Wazer DE, Hepel JT, Leonard KL. *BRCA1* mutations associated with increased risk of brain metastases in breast cancer: a 2:1 matched-pair analysis. Int J Radiat Oncol Biol Phys 2016;96(2s):S59–60.
[6] Albiges L, André F, Balleyguier C, Gomez-Abuin G, Chompret A, et al. Spectrum of breast cancer metastasis in *BRCA*1 mutation carriers: highly increased incidence of brain metastases. Ann Oncol 2005;16(11):1846–7.
[7] Musolinio A, Ciccolallo L, Panebianco M, Fontana E, Zanoni D, Bozzetti C, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. Cancer 2011;117(9):1837–46.
[8] Hu J, Kesari S. Strategies for overcoming the blood-brain barrier for the treatment of brain metastases. CNS Oncol 2013;2(1):87–98.
[9] Zhang S, Lin QD, DI W. Suppression of human ovarian carcinoma metastasis by the metastasis-suppressor gene, BRMS1. Int J Gynecol Cancer 2006;16(2):522–31.
[10] Seraj MJ, Samant RS, Verderame MT, Welch DR. Functional evidence for a novel human breast carcinoma metastasis suppressor, *BRMS1*, encoded at chromosome 11q13. Cancer Res 2000;60:2764–9.
[11] Sheng XJ, Zhou DM, Liu Q, Lou SY, Song QY, Zhou YQ. BRMS1 inhibits expression of NF-kappaB subunit p65, uPA and OPN in ovarian cancer cells. Eur J Gynaecol Oncol 2014;35(3):236–42.
[12] Silver DP, Livingston DM. Mechanisms of BRCA1 tumor suppression. Cancer Discov 2012;2(8):679–84.
[13] Pacheco TR, Fernandes AC, Ali SM, Maia-Matos M, Gaspar Gomes da Costa AL, Abreu C, et al. Activation of PI3K/AKT/mTOR pathway in ER+ breast cancer: Analysis of paired primary and metastatic tumor samples. J Clin Oncol. ASCO Annual Meeting Proceedings 2015;33(15). https://doi.org/10.1200/jco.2015.33.15_suppl.577. abst 577.
[14] Shen Q, Sahin AA, Hess KR, Suki D, Aldape KD, Sawaya R, et al. Breast cancer with brain metastases: clinicopathologic features, survival, and paired biomarker analysis. Oncologist 2015;20(5):466–73.
[15] Medress Z, Gephart HM. Molecular and genetic predictors of breast-to-Brain metastasis: review and case presentation. Cureus 2015;7(1):e246.
[16] Hayashi N, Niikura A, Masuda N, Takashima S, Nakamura R, Watanabe K, et al. Prognostic factors of HER-2 positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis. Breast Cancer Res Treat 2015;149(1):679–84.
[17] Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012;30(6):593–9.
[18] Porzio G, Ronzino G, Farina E, Aielli F, Ficorella C, Marchetti P. Cerebral metastasis from ovarian cancer treated with a multidisciplinary approach. Case report and review of literature. Eur J Gynaecol Oncol 2003;24(6):563–4.
[19] Geisler JP, Geisler HE. Brain metastases in epithelial ovarian carcinoma. Gynecol Oncol 1995;57:247–9.
[20] Stanisławiak J, Lubin J, Markowska J. Brain metastases from epithelial ovarian cancer-report of cases. Eur J Gynaecol Oncol 2009;30(6):683–5.
[21] Chuang TC, Hsu SC, Cheng YT, Shao WS, Wu K, Fang GS, et al. Magnolol down-regulates HER2 gene expression, leading to inhibition of HER2-mediated metastatic potential in ovarian cancer cells. Cancer Lett 2011;311(1):11–9.
[22] Sekine M, Yoshihara K, Komata D, Haino K, Nishino K, Tanaka K. Increased incidence of brain metastases in BRCA1-related ovarian cancers. J Obstet Gynaecol Res 2013;39(1):292–6.
[23] Ciucci A, Zannoni GF, Travaglia D, Petrillo M, Scambia G, Gallo D. Prognostic significance of the estrogen receptor beta (ERβ) isoforms ERβ1, ERβ2, and ERβ5 in advanced serous ovarian cancer. Gynecol Oncol 2014;132(2):351–9.
[24] Kucia M, Jankowski K, Reca R, Wysoczynski M, Bandura L, Allendorf DJ, et al. CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion. J Mol Histol 2004;35(3):233–45.
[25] Hall JM, Korach KS. Stromal cell-derived factor-1, a novel target of estrogen receptor action, mediates the mitogenic effects of estradiol in ovarian and breast cancer cells. Mol Endocrinol 2003;17:792–7.
[26] Aravindan BK, Prabhakar J, Somanathan T, Subhadra L. The role of chemokine receptor 4 and its ligand stromal cell derived factor 1 in breast cancer. Ann Transl Med 2015;3(2):23.
[27] Emdad L, Sarkar D, Su ZZ, Lee SG, Kang DC, Bruce JN, et al. Astrocyte elevated gene-1: recent insights into a novel gene involved in tumor progression, metastasis and neurodegeneration. Pharmacol Ther 2007;114(2):155–70.
[28] Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: american Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2014;138(2):241–56.
[29] Liu L, Wu J, Ying Z, Chen B, Han A, Liang Y, et al. Astrocyte elevated gene-1 up-regulates matrix metalloproteinase-9 and induces human glioma invasion. Cancer Res 2010;70(9):3750–9.
[30] Li C, Liu J, Lu R, Yu G, Wang X, Zhao Y, et al. AEG -1 overexpression: a novel indicator for peritoneal dissemination and lymph node metastasis in epithelial ovarian cancers. Int J Gynecol Cancer 2011;21(4):602–8.
[31] Li G, Guo X, Tang L, Chen M, Luo X, Peng L, et al. Analysis of *BRCA*1/2 mutation spectrum and prevalence in unselected Chinese breast cancer patients by next-generation sequencing. J Cancer Res Clin Oncol 2017;143(10):2011–24.
[32] Laudanski P, Swiatecka J, Kozlowski L, Leśniewska M, Wojtukiewicz M, Wołczyński S. Increased serum level of membrane type 1-matrix metalloproteinase (MT1-MMP/MMP-14) in patients with breast cancer. Folia Histochem Cytobiol 2010;48(1):101–3.
[33] Jarzabek K, Laudanski P, Dzieciol J, Dabrowska M, Wołczyński S. Protein kinase C involvement in proliferation and survival of breast cancer cells. Folia Histochem Cytobiol 2002;40(2):193–4.
[34] Marchetti C, Ferrandina G, Cormio G, Gambino A, Cecere S, Lorusso D, et al. Brain metastases in patients with EOC: Clinicopathological and prognostic factors. A multicentric retrospective analysis from MITO group (MITO 19). Gynecol Oncol 2016;143(3):532–8.
[35] Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline *BRCA1* and *BRCA2* mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001;68:700–10.
[36] Bell D, Berchuck A, Birrer M, Chien J, Cramer D, Dao F, et al. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474(7353):609–15.
[37] Hurst DR, Xie Y, Vaidya KS, Mehta A, Moore BP, Accavitti-Loper MA, et al. Alterations of BRMS1 ARID 4A interaction modify gene expression but still suppress metastasis in human breast cancer cells. J Biol Chem 2008;283(12):7438–44.