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The Histopathological Findings of High-grade Serous Ovarian Carcinomas in Patients with BRCA Germline Mutations, Single Center Experience

BRCA Germline Mutasyonu Olan Hastalarda Yüksek Dereceli Seröz Over Karsinomlarının Histopatolojik Özellikleri; Tek Merkez Deneyimi

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Abstract

Objective: The current study aims to contribute to the identification of distinctive histomorphological findings of BRCA-associated high-grade ovarian carcinomas.

Methods: The study was planned to include high-grade serous carcinoma cases diagnosed in 2020-2021. The histopathological features of the groups with and without BRCA mutation were evaluated comparatively in the tumor slides of the cases.

Results: Solid/pseudo-endometrioid/transitional cell carcinoma-like growth pattern and high mitotic rates were observed more frequently in the BRCA mutation group than in those without mutations, which was statistically significant. There was no significant difference between the two groups in terms of significant nuclear pleomorphism, frequency of necrosis, and prominent tumor infiltrating lymphocytes.

Conclusion: Pathologists may play a crucial role in detecting BRCA mutations in patients without a family history of carcinoma. In this respect, it should be kept in mind that BRCA mutations may be present in high-grade serous ovarian carcinoma cases with solid/pseudo-endometrioid/transitional carcinoma-like growth pattern, necrosis, prominent nuclear pleomorphism, high mitotic activity and prominent tumor-infiltrating lymphocytes.

Keywords: BRCA, high-grade serous ovarian cancer, histopathology

Öz

Amaç: Çalışmamız BRCA ile ilişkili yüksek dereceli over karsinomlarının ayırt edici histomorfolojik bulgularının belirlenmesine katkı sağlamayı amaçlamaktadır.

Yöntem: Çalışma 2020-2021 yıllarında tanı alan yüksek dereceli seröz karsinom olgularını kapsayacak şekilde planlanmıştır. BRCA mutasyonu saptanan ve saptanmayan gruplarda histopatolojik özellikler arşivden tümör lamları çıkarılarak karşılaştırmalı olarak değerlendirilmiştir.

Bulgular: Solid/psödo-endometrioid/transizyonel karsinom benzeri büyüme paterni ve yüksek mitoz sayısı BRCA mutasyonu olan grupta mutasyon olmayanlara göre istatistiksel açıdan anlamlı olacak şekilde daha sık izlenmiştir. Belirgin nükleer pleomorfizm, nekroz sıklığı, belirgin tümör infiltre edici lenfositler açısından iki grup arasında anlamlı fark bulunmamıştır.

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Öz

Sonuç: Ailesinde karsinom öyküsü olmayan hastalarda BRCA mutasyonlarının saptanmasında patologlar çok önemli bir rol oynayabilir. Bu açıdan solid/psödo-endometrioid/transizyonel karsinom benzeri büyüme paterni, nekroz, belirgin nükleer pleomorfizm, yüksek mitotik aktivite ve belirgin tümör infiltre edici lenfositler gösteren yüksek dereceli seröz over karsinom olgularında BRCA mutasyonları olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: BRCA, yüksek dereceli seröz yumurtalık kanseri, histopatoloji

Introduction

Germline BRCA1 or BRCA2 mutations are detected in approximately 15% of all ovarian epithelial neoplasia patients[1]. The distinctive histopathological diagnosis of ovarian cancer associated with hereditary breast and ovarian cancer syndrome (HBOC) due to BRCA mutations is high-grade serous carcinoma (HGSC), and the frequency of BRCA1 and BRCA2 germline mutations increases to approximately 25% in patients diagnosed with these neoplasms[1-3]. The detection rate of somatic mutations is around 3-7%[4,5]. Apart from the BRCA genes, several other tumor suppressor genes and oncogenes are associated with hereditary ovarian cancer.

Tumor cells that have homologous recombination deficiency show high sensitivity to platinum-based chemotherapy regimens, and these tumors can be treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors. PARP inhibitors are a new treatment option that has been reported to prolong progression-free survival in patients with HGSC, particularly those with BRCA1 and BRCA2 mutations[6-8]. To determine which HGSC patients are likely to carry BRCA1 or BRCA2 mutations will provide cost-effective results for genetic testing applications.

Previous studies have shown a relationship between BRCA status and histological growth pattern, nuclear pleomorphism, necrosis, mitotic rates, and tumor-infiltrating lymphocytes (TILs) in breast tumors and high-grade serous ovarian tumors[9-12].

This study, examining patients with HGSC who applied to our center, was conducted to contribute to the definition of the distinctive histomorphological features of tumors associated with BRCA mutation.

Materials and Methods

Between January 1, 2020 and December 31, 2021, the records of patients diagnosed with HGSC in our institution were examined and 130 patients were identified. Among these cases, 72 patients for whom BRCA1/2 hereditary cancer risk panel could not be applied, 12 patients whose primary tumor was not of ovarian origin, and 20 patients who received neoadjuvant chemotherapy were excluded from the study. Twenty-six patients whose primary tumor originated from the ovary and who underwent genetic analysis were included in the study. Germline BRCA1 mutation was found in 6 of the patients, and BRCA2 mutation was found in 3.

Tumor slides of the cases were re-evaluated by a specialist pathologist (GA). Evaluation was made from the primary tumor localization (ovary). Metastatic foci were not included in the evaluating slides. Tumor growth patterns were assessed in terms of the architectural features of the tumor. Cases showing solid, pseudo endometrioid, and transitional cell carcinoma-like (SET) features more than 25% were noted as positive for SET morphology[9,13]. When more than one SET patterns were together, the ratios were summed and the calculation was made.

Initially, tumor slides were evaluated at low magnification (x40) for necrosis (comedo-like or geographic), nuclear pleomorphism, mitotic index, TILs, and tumor growth patterns. Tumors containing comedo-like or geographic necrosis were evaluated for the presence of necrosis. Marked nuclear pleomorphism has been determined as a prominent nuclear aberration in tumor cells compared to the surrounding tissue, such as clear irregular nuclear contours, vesicular nuclei, hyperchromatic, bizarre or coiled nuclei, macronucleoli, abundant eosinophilic cytoplasm)[14]. It was considered as positive when necrosis and nuclear pleomorphism were easily detectable in the majority of slides[9,14].

Although there are various publications on the mitotic rate and TILs evaluation in ovarian cancers, definite criteria have not been determined. In the literature review, it was seen that the criteria determined in breast cancers tend to be used in general. Mitotic rate assessment was made according to the modified Nottingham grading system. Accordingly, in

the evaluator microscope with a field diameter of 0.65 mm, mitosis was counted in 10 consecutive high magnification fields (400x) in the most mitotic active area of the tumor and scored as low (≤12)/medium (13-24)/high (≥25)[14]. Mononuclear infiltrate within the borders of the invasive tumor was taken into account while performing TILs evaluation. Lymphocytes in the intercellular areas and cores of the papillary structures of the tumor were included in the count. Immune infiltrates outside the tumor margins, areas of tumor necrosis, and lymphocytes within the blood vessels were excluded. Prominent TILs were considered positive when >40 intraepithelial lymphocytes in a single high-power field[14].

Ethics committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2021/11, date: 11.2021).

Statistical Analysis

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of the variables. Quantitative variables are shown in the tables as mean ± standard deviation and median range (maximum-minimum), while categorical variables are shown as n (%). The Mann-Whitney U test was used in the comparison of two independent groups in which quantitative data were evaluated. Fisher's Exact test was used to compare categorical variables in which qualitative data were evaluated. The results of the analysis were accepted as significant with a p-value less than 0.05 at a confidence level of 95%.

Results

The descriptive and histopathological features of the cases included in the study are presented in Table 1. The mean age of the group was 53.9 (±10.5). It was observed that 34.6% of the included cases had *BRCA* gene mutations; 66.7% of those with mutations are BRCA1 and 33.3% are BRCA2. Considering the tumor location, it was determined that 61.5% were bilateral and 38.5% were unilateral. While 26.9% of the patients showed extraovarian spread, it was observed that capsular rupture was observed in 50% of them. Lymph node metastasis was observed in 42.3% of the cases. Considering the histopathological features, SET growth pattern was detected in 65.4% of the cases (Figures 1, 2). Significant nuclear pleomorphism is present in 69.2% of cases. The proportion of tumors with significant mitotic activity was 34.6%; the rate of tumors with significant TILs is 23.1%. Necrosis was detected

Table 1. Descriptive clinical and histopathological features of the cases included in the study

	Count	%
BRCA mutation		
Present	9	34.6
Absent	17	65.4
BRCA mutation type		
BRCA-1	6	66.7
BRCA-2	3	33.3
Capsule rupture		
Present	13	50.0
Absent	13	50.0
Lymph node metastasis		
Present	11	42.3
Absent	15	57.7
Lymphovascular invasion		
Present	16	61.5
Absent	10	38.5
Necrosis		
Present	14	53.8
Absent	12	46.2
High mitotic activity		
Present	9	34.6
Absent	17	65.4
Extraovarian spread		
Present	7	26.9
Absent	19	73.1
SET pattern		
Present	17	65.4
Absent	9	34.6
Significant TILs		
Present	6	23.1
Absent	20	76.9
Ovarian side		
Unilateral	10	38.5
Bilateral	16	61.5
Prominent nuclear pleomorphism		
Present	18	69.2
Absent	8	30.8
Total	**26**	**100.0**

TILs: Tumor-infiltrating lymphocytes, SET: Solid, pseudo endometrioid

in 53.8% of the cases and lymphovascular invasion was found in 61.5% of the cases.

The histopathological features of the groups with and without *BRCA* gene mutation are given in Table 2. While 66.7% of the tumors are bilateral in the group with *BRCA* gene mutation, this rate is 58.8 in the group without mutation. There was no statistically significant difference in tumor localization in the group with and without *BRCA* gene mutation. Extraovarian spread was observed more frequently in the group with mutations (77.8%), but there was no statistically significant difference between the group without mutation (70.6%). The frequency of capsular rupture was also seen more frequently in the group with mutation (55.6%) than in the group without (47.1%), but it was not statistically significant. The frequency of lymph node metastases was not statistically different in the group with and without *BRCA* gene mutation.

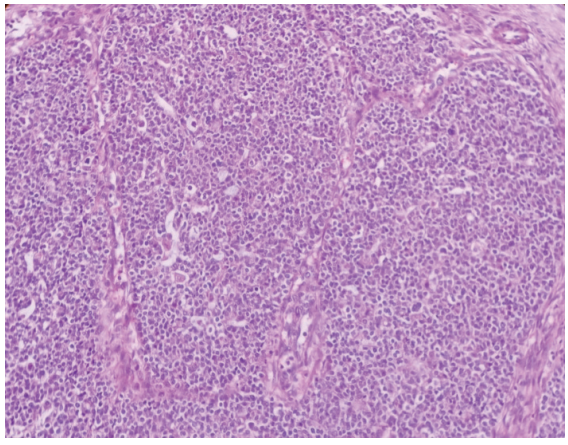

Figure 1. Solid growth pattern in one case with BRCA mutation

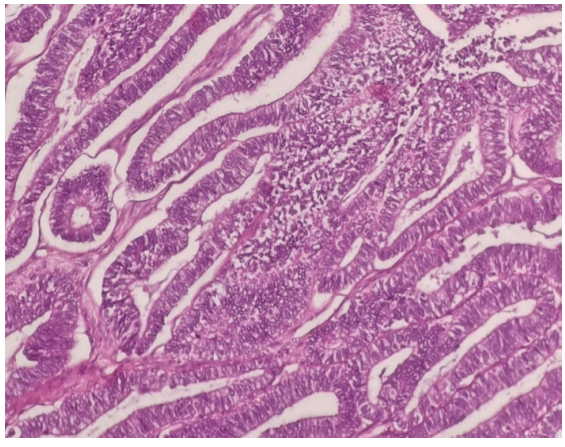

Figure 2. Pseudo-endometrioid growth pattern in one case with BRCA mutation

SET growth pattern was observed with a frequency of 66.7% in the group with *BRCA* gene mutation, and this rate was 17.6% in the group without gene mutation. The difference between the two groups was statistically significant (p=0.02). Marked nuclear pleomorphism was observed at a frequency of 88.9% and 58.8% in the group with and without *BRCA* gene mutation, respectively. However, this difference is not statistically significant. High mitotic activity was observed more frequently in the group with *BRCA* gene mutation (66.7%) than in the group without mutation (17.6%), which was statistically significant (p=0.02). Prominent tumor infiltrating lymphocytes were observed at a rate of 22.2% in the group with *BRCA* gene mutation, while it was observed at a rate of 23.5% in the group without mutations. This difference is not statistically significant. The incidence of necrosis was 55.6% in the group with *BRCA* gene mutation and 52.9% in the group without mutation. Although lymphovascular invasion was observed more frequently in the mutation group (77.8%), this difference was not statistically significant.

Discussion

Ovarian cancer ranks 8th among the causes of cancer-related death in women worldwide[15]. Epithelial ovarian tumors constitute 95% of all ovarian tumors[16]. Histological subtypes of epithelial ovarian tumors, in order of frequency; HGSC (75%), low-grade serous carcinoma (10%), endometrioid

Table 2. Histopathological features according to *BRCA* gene mutation status

		***BRCA* gene mutation**		
		Present	**Absent**	
		%	**%**	***p**
Capsule rupture	Present	55.6	47.1	0.50
Lymph node metastasis	Present	55.6	35.3	0.19
Lymphovascular invasion	Present	77.8	52.9	0.39
Necrosis	Present	55.6	52.9	0.61
Prominent nuclear pleomorphism	Present	88.9	58.8	0.19
High mitotic activity	Present	66.7	17.6	**0.02**
Extraovarian spread	Present	77.8	70.6	0.53
SET	Present	66.7	17.6	**0.02**
Significant TILs	Absent	77.8	76.5	0.66
	Present	22.2	23.5	

TILs: Tumor-infiltrating lymphocytes, SET: Solid, pseudo endometrioid, and transitional cell carcinoma-like

carcinoma (10%), clear cell carcinoma (5%), and mucinous carcinoma (2.4%)[16].

BRCA1 and BRCA2 are the most common mutations in HGSC. Together with *BRCA1* and *BRCA2*, *ATM*, *BARD1*, *NBN* and some other genes, they are important elements of the homologous recombinant (HR) DNA repair system[17]. Germline and somatic mutations in *HR* genes are seen in approximately 30% of patients with ovarian cancer, while 75% of them are in *BRCA1* and *BRCA2* genes[18]. 54-74% of BRCA1/2 mutations are germline and 27-46% are somatic type[4,5,17,19].

BRCA1 and *BRCA2* genes are located in chromosome 17q21 and 13q 12.3 regions, respectively, and are tumor suppressor genes that have important roles in DNA repair, cell cycle checkpoints, protein ubiquinization and chromatin rearrangement[20-22]. They encode proteins required for DNA double-strand break repair by HR[23,24]. Mutations across both genes are widely distributed. "Second hit" cells that cause HR repair deficiency in women with HBOC rely on error-prone alternative DNA repair mechanisms that lead to an increased risk of developing various malignancies, including the ovary and breast, as well as the tuba uterina and peritoneum[25]. Tumor cells showing HR repair deficiency show high sensitivity to platinum-based chemotherapy regimens, and these tumors can be treated with PARP inhibitors. PARP inhibitors are a new treatment option that has been reported to prolong progression-free survival in patients with HBOC, especially those with BRCA1 and BRCA2 mutations[6-8]. Besides BRCA1/2 mutations, other mutations in homologous recombination repair (*HRR*) genes such as RAD51, ATM, ATR, BRIP1, PALB2, RB1, NF1, CDKN2A confer homologous recombination deficiency and increased susceptibility to PARP inhibitors. HGSCs are associated with recurrent somatic mutations in the *NF1*, *BRCA1*, *BRCA2*, *RB1* and *CDK12* genes at a rate of approximately 5-8%[16].

Detection of BRCA mutation creates important prognostic and predictive effects in patients with HGSC. Current guidelines recommend a number of approaches to molecular testing. Guidelines from working groups such as the National Comprehensive Cancer Council and the American Society of Clinical Oncology (ASCO) recommend that all patients diagnosed with epithelial ovarian cancer undergo germline genetic testing at diagnosis for the *BRCA1/2* genes as well as other known ovarian cancer susceptibility genes[26,27]. ASCO also recommends that patients without germline BRCA1/2 mutations undergo genetic tumor testing for somatic mutations in BRCA1/2 and other commonly mutated genes[27]. The Society of Gynecological Oncology recommends the BRCA1/2 test for all patients with epithelial ovarian, tuba uterine and peritoneal cancers, even if there is no family history[28]. Joint guidelines of the European Society of Gynecological Oncology and the European Society of Medical Oncology recommend BRCA1/2 mutation testing for all patients with non-mucinous ovarian cancer[29].

Although it is recommended to apply genetic testing to all patients diagnosed with ovarian cancer, from a cost/effectiveness perspective, evaluating patients in terms of BRCA mutation risk and identifying patients who will benefit most from testing may be the ideal management plan. One way to classify patients, other than family history, is tumor histomorphology. For BRCA-associated ovarian tumors, the characteristic histopathological findings need to be better defined. As the identification of these morphological features increases, it becomes easier to predict which ovarian cancer cases may have BRCA1 and/or 2 mutations during routine pathological examinations. Similarly, reporting morphology suspicious for BRCA1 and/or 2 mutations in pathology reports may facilitate and accelerate clinical-genetic studies on a case-by-case basis.

Soslow et al.[9] examined tumors from patients with germline BRCA1/2 mutations in addition to tumors with somatic BRCA1/2 mutations or promoter hypermethylation. That study described a distinct morphological pattern, defined as SET morphology, in tumors with BRCA mutations. This morphological appearance consists of "solid", "pseudo-endometrioid" and "transitional cell carcinoma-like" patterns. Defined histologically, the solid pattern consists of large tumor islands without a specific growth pattern. In the pseudo-endometrioid pattern, gland-like structures composed of tubular cells and round cavities forming a cribrifoming-like appearance are observed. The transitional cell carcinoma-like type includes tumor cells that form an insular or trabecular architecture similar to the epithelium of the bladder[9,13]. According to this study, it was determined that BRCA1-associated HGSCs showed high mitotic rates, prominenet TILs, geographic/comedo-type necrosis and SET features, while tumors with BRCA2 mutations had SET features but tended to show relatively lower rates of TILs and necrosis.

Tubo-ovarian carcinomas in a cohort of BRCA1 germline mutation carriers [Fujiwara et al.[14]]; it has been shown that it tends to exhibit high-grade and serous/undifferentiated

histology, prominent TILs, marked nuclear atypia with giant/bizarre forms, and abundant mitotic figures.

In this study, which was conducted to compare the histopathological features according to the *BRCA1/2* gene mutation status in HGSCs of the ovary, 130 patients who applied to our center for a year were evaluated. *BRCA1/2* gene mutations were detected in more than a quarter of the patients who underwent genetic analysis. This rate was found to be compatible with previous studies[30-32].

In this study, SET growth pattern was found to be significantly higher in the group with BRCA mutation. In the study of Soslow et al.[9] in which BRCA1/2 mutations were examined, it was shown that HGSCs associated with BRCA1 and BRCA2 mutations tended to show SET features at a high rate[20].

In our study, mitotic activity was found to be high in patients with BRCA1/2 mutation according to the Nottingham grading system, which is consistent with the literature. In a study conducted in Canada in 2020 by Fujiwara et al.[14], who evaluated mitotic activity according to the same grading system, it was shown that ovarian carcinomas carrying BRCA mutations tend to exhibit significant mitotic activity[14,20]. Similarly, Soslow et al.[9] found high mitotic rates in their studies in which they examined HGSCs carrying the BRCA1/2 mutation.

It has been reported in many studies that HGSCs carrying BRCA1 mutations contain significant TILs[9,14,20]. In this sense, when we examined our cases, TILs were detected in all tumors, but when the groups with and without mutations were compared, no significant difference was found between the groups in terms of prominent TILs.

The prominent nuclear pleomorphism observed in tumor cells is defined as a characteristic histological feature in HGSC with BRCA mutation[9,14]. In our study, marked nuclear pleomorphism was found at a higher rate in the group with BRCA mutation than in the group without it. However, the difference was not significant. This may be because the study group was small.

The presence of necrosis is one of the more frequently expected characteristic findings, especially in HGSCs carrying the BRCA1 mutation[9]. In our study, necrosis was found to be slightly higher in the group carrying the BRCA mutation, but the difference was not significant.

Study Limitations

The fact that genetic analysis could not be performed on all patients diagnosed with HGSC in this study was a limiting factor. We think that the more detailed and reliable evaluation of the characteristic histopathological features described in the literature in HGSCs carrying *BRCA1/2* gene mutations may be possible by increasing the number of cases.

Conclusion

The pathologists play a key role in detecting cases with BRCA mutations, while they examine the tumor morphology, microscopically. It is particularly important for cases with no family history for carcinoma. In this respect, it should be kept in mind that high grade serous ovarian carcinoma cases that show SET pattern, necrosis, prominent nuclear pleomorphism, high mitotic activity and TIL may have BRCA mutations.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Commitee (decision no: 2021/11, date: 11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: İ.Ç., Concept: C.K.T., Design: G.A., C.K.T., Data Collection or Processing: G.A., Ö.Ö.K., T.R.Ö., Analysis or Interpretation: G.A., C.K.T., Literature Search: G.A., Writing: G.A.

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