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Invasion Patterns of Metastatic Extrauterine High Grade Serous Carcinoma with *BRCA* Germline Mutation and Correlation with Clinical Outcomes

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Abstract

Characteristic histopathologic features have been described in high grade serous carcinoma associated with *BRCA* abnormalities (HGSC-*BRCA*), which are known to have relatively favorable clinical outcomes. The aim of this study was to evaluate the clinical significance of invasion patterns in metastatic HGSC-*BRCA* cases. Thirty-seven cases of advanced stage HGSC with known *BRCA1* or *BRCA2* germline mutation were retrieved from our institutional files. Twenty-three patients had germline mutation of *BRCA1* and 14 with *BRCA2* mutation. The pattern of invasion at metastatic sites was recorded and classified as pushing pattern (either predominantly or exclusively), an exclusively micropapillary infiltrative pattern, or an infiltrative pattern composed of papillae, micropapillae, glands and nests (mixed infiltrative pattern). Histologic evaluation of metastases was performed without knowledge of genotype or clinical outcome. Clinical data were abstracted from medical records. Median age was 56 years (range, 31-73 years). All patients presented at stage IIIC or IV and underwent complete surgical staging followed by chemotherapy. All 37 HGSC-*BRCA* cases showed either pushing pattern metastases (30; 81%) or infiltrative micropapillary metastases (7; 19%). No HGSC-*BRCA* cases exhibited metastases composed solely of mixed infiltrative patterns. Among the 7 infiltrative micropapillary cases, 6 had *BRCA1* germline mutation vs 1 *BRCA2*. Median time of follow-up was 26 months (range, 13-49 months). All 7 patients with infiltrative micropapillary metastases either experienced recurrence or died of disease (5 recurrence and 2 deaths), which was significantly worse than

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patients with predominantly pushing pattern metastases, of whom 16 of 30 (53%) experienced recurrence (n=14) or died of disease (n=2); P value= 0.03.

In conclusion, the recognition of different invasion patterns of metastatic extrauterine HGSC-*BRCA* has prognostic implications. The infiltrative micropapillary pattern is associated with poor outcomes and is more frequently seen in *BRCA1* associated HGSC than in *BRCA2* cases.

Keywords

BRCA; invasion; clinical outcome; ovary; serous carcinoma; epithelial ovarian cancer

Introduction

High grade serous carcinomas of the uterine adnexa with *BRCA* deficiency (HGSC-*BRCA*) have recently been described to demonstrate characteristic histopathologic features including solid, pseudoendometrioid, transitional cell-like growth patterns (SET pattern), high mitotic index, numerous tumor infiltrating lymphocytes, and severe nuclear atypia^{1,2}.

Our group has also recently shown that HGSC-*BRCA* exhibit characteristic morphologic features in metastatic sites. Reyes et al showed that all studied cases with *BRCA1* or *BRCA2* abnormalities showed either a pushing pattern of omental involvement, (76% of cases), or a purely micropapillary infiltrative metastatic pattern (24% of cases). In contrast, all HGSC cases lacking *BRCA* alterations showed infiltrative metastases containing combinations of growth patterns including papillae, micropapillae, glands, and nests (a mixed infiltrative pattern)³.

HGSC-*BRCA* has been reported to be associated with relatively better clinical outcomes compared to HGSC without *BRCA* deficiency. This is partly because of increased sensitivity to chemotherapy, and also possibly due to the tendency to spread in the form of circumscribed, rounded metastases amenable to optimal debulking. Furthermore, it has been reported recently that HGSC patients with *BRCA2* mutation have better survival compared to *BRCA1* mutated and *BRCA* non-mutated patients⁴⁻⁶.

In this study, we hypothesize that the pattern of invasion at metastatic sites has clinical significance in patients with metastatic HGSC-*BRCA*.

Materials and Methods

Thirty-seven cases of advanced stage HGSC with known *BRCA1* or *BRCA2* germline mutation were retrieved from the archives of the Department of Pathology at Memorial Sloan Kettering Cancer Center, after obtaining institutional review board approval. These patients had undergone germline genetic testing per the policies of the Gynecology Disease Management Team at Memorial Sloan Kettering Cancer, which strives to offer testing to all patients diagnosed with high-grade serous carcinoma of peritoneum, ovary and fallopian tube. Patient anonymity was maintained. These cases were accessioned between 2009 and 2012 and were exclusive of previously reported cases.^{1,3} Of 37 cases, 23 had *BRCA1* germline mutation and 14 had *BRCA2* germline mutation.

All patients presented at advanced stage (FIGO stage IIIC [n=26] or IV [n=11]) and underwent surgical staging followed by chemotherapy. All but 2 patients had an optimal debulking surgery. Nineteen patients were treated with intravenous and intraperitoneal chemotherapy, while the remaining 18 patients were treated only intravenously. Chemotherapy consisted of a platinum-containing agent and a taxane in all cases. All available hematoxylin & eosin slides from metastatic sites were reviewed. The median number of slides reviewed was 14, with a minimum number of 3 slides. Diagnosis as HGSC was based upon Gilks' modification to the WHO criteria for diagnosing HGSC.⁷ Gilks' modification classifies high grade ovarian carcinomas as HGSC for cases showing solid, cribriform, microcystic, and transitional cell-like architectural patterns as long as confirmatory endometrioid features such as squamous metaplasia, endometrioid adenofibroma, associated endometriosis, and synchronous endometrioid carcinoma of endometrium are absent. The presence of radially oriented slit-like spaces, scattered bizarre mononuclear giant cells, nuclear pleomorphism, and a high mitotic index are characteristic and found at least focally in nearly every case.

Each metastatic site was evaluated for types of peritoneal invasion patterns. Two general patterns were distinguished, a pushing pattern (Fig 1), in which the interface between tumor and adipose tissue was rounded, linear, and/or smooth, and an infiltrative pattern (Fig 2) that was characterized by irregular permeation of adipose tissue. Rules for distinguishing invasive and non-invasive implants serous borderline tumor are similar.⁸ The irregularly infiltrative patterns were further subdivided by architecture, with one pattern consisting of infiltrative micropapillae only (Figs 2A and 2B) and another pattern showing infiltrating by combinations of papillae and micropapillae and, in some cases, glands and solid tumor (mixed pattern; Fig 2C).³ When different metastatic sites featured different patterns, the predominant pattern was recorded. In a hypothetical case containing 5 metastatic sites, a case was considered "pushing pattern" if 3, 4 or 5 metastatic sites displayed this pattern.

Tumor architectural growth patterns were also studied. Micropapillary tumor displayed dyshesive aggregates of tumor cells lacking central vascular cores surrounded by retraction space (Figs 2A and 2B). Papillary architecture was defined as tumor cells arranged around finger-like vascular cores (Fig 3A). Solid architecture was defined as tumor cells arranged in sheets (Fig 3B). Pseudoendometrioid (cribriform architecture) was defined as tumor growing in back to back nests with punched out microlumens (Fig 3C). Transitional cell-like was characterized by broad papillae with thick, stratified layers of tumor cells (Fig 3D). Solid, pseudoendometrioid and transitional cell-like growth patterns constitute the SET pattern (Figs 3B-D).

Clinical data were abstracted from medical records. Histologic evaluation of metastases was performed without knowledge of genotype or clinical outcome. Appropriate statistical tests were performed.

Results

The mean age of our cohort was 56 years (range, 32-76 years). The number of metastatic sites ranged from 1 to 10 and included omentum, serosa of sigmoid, appendix, small bowel, bladder, gall bladder, pelvic sidewall, diaphragm, and cul-de sac.

All 37 HGSC-*BRCA* cases showed either pushing pattern, defined by the predominant pattern found in cases with multiple metastatic sites, or infiltrative micropapillary metastases (Fig 4). Thirty of 37 cases demonstrated either an exclusive or predominant pushing pattern, while the remaining 7 cases exhibited only infiltrative micropapillary metastases. Of the 30 pushing pattern cases, 17 showed pushing patterns in each metastatic site (exclusively pushing pattern). Fourteen of the 17 exclusively pushing pattern cases exhibited a solid or transitional cell-like architectural component; 8 were purely solid or transitional cell-like, 4 had combinations of solid, papillary, micropapillary, and pseudoendometrioid patterns, and 2 had combinations of solid and papillary patterns. The remaining exclusively pushing pattern metastases were purely papillary (n=1), purely glandular (n=1), or mixed papillary and micropapillary (n=1). Thirteen cases featured a predominance of pushing pattern metastases along with smaller numbers of destructively infiltrating metastases featuring combinations of solid, papillary and micropapillary architecture (mixed pattern). Among these 13 cases, the percentage of pushing pattern metastases amongst all metastases ranged from 57% to 80% (median, 67%). No case exhibited only mixed pattern metastases comprising papillae and micropapillae with or without solid, transitional cell-like or pseudoendometrioid patterns. The mean age of patients with pushing pattern metastases was 56 yrs (range, 44-68 years), while those with infiltrative micropapillary metastases were, on average, 54 years (range, 32-77 years), differences that were not statistically significant.

The distribution of invasion patterns and tumor architecture in metastatic sites, stratified by the genetic subgroup, is illustrated in Table 1. Among the 23 *BRCA1* germline mutation cases, 17 cases had pushing pattern metastases, showing in decreasing frequency, solid, papillary, and pseudo- endometrioid tumor architecture. Regarding the *BRCA2* patients, pushing pattern metastases showing solid and papillary architecture were seen in all cases except one. Overall, among the 7 infiltrating micropapillary cases, 6 had *BRCA1* germline mutation vs 1 *BRCA2*, suggesting that infiltrating micropapillary cases are enriched for *BRCA1* patients.

The median follow-up time was 26 months (range, 13-49 months). All 7 infiltrating micropapillary cases patients either experienced recurrence or died of disease (5 recurrences and 2 deaths), which was significantly worse than patients with pushing pattern metastases, only 16 of 30 (53%) of whom experienced recurrence (n=14) or died of disease (n=2); *P* value= 0.03.

Discussion

The data presented here validate previously reported associations between *BRCA* germline mutation and HGSCs with solid, pseudo-endometrioid and transitional cell-like growth patterns (SET pattern) with pushing pattern metastasis in the form of rounded tumor nodules

lacking destructive invasion at their periphery.³ Novel findings include the greater prevalence of metastatic HGSCs with pushing pattern metastases among *BRCA2* mutations carriers as compared with *BRCA1* mutations carriers. Only 1/14 *BRCA2* metastases showed an exclusively micropapillary infiltrative pattern, compared to 6/23 *BRCA1* germline cases. Last, we show that patients with pushing pattern metastases have significantly better clinical outcomes than patients with destructively invasive metastases at a median follow-up of 26 months. Previously reported relationships between genomically defined subsets of HGSC⁹ and morphology, platinum sensitivity, and clinical outcome suggest that our data could explain relatively favorable clinical outcomes in patients with “transitional cell carcinoma of ovary”⁵ and/or who carry *BRCA* germline mutations⁶.

Invasion patterns and clinical outcomes in gynecologic carcinomas

The relationship between invasion patterns and clinical outcomes has been the subject of recent publications. With specific reference to gynecologic carcinomas, poor clinical outcomes or high-stage disease is reportedly associated with certain destructively invasive squamous carcinomas of the cervix¹⁰ and with microcystic, elongated and fragmented (MELF)-invasive endometrioid carcinoma.¹¹ Meanwhile, endometrioid adenocarcinomas that have a pushing pattern of invasion¹² and human papilloma virus-associated endocervical adenocarcinomas with a highly differentiated glandular pattern of invasion lacking a stromal response^{13,14} are reportedly associated with favorable clinical outcomes. It was also previously reported that many “transitional cell carcinomas” of the ovary metastasize to the peritoneum in the form of small, rounded nodules that were more amenable to surgical debulking than tumor showing other invasion patterns.⁵ These tumors often display enhanced platinum sensitivity and relatively favorable clinical outcomes. There is a growing consensus that high grade “transitional cell carcinomas” of the ovary^{15,16,17} are HGSC variants^{18,19,20} and this is reflected in the 2014 World Health Organization classification of gynecologic tumors.²¹ With respect to HGSC, the Dr Elvio Silva's group reported an abstract in which patients with HGSCs showing invasion patterns similar to the infiltrative micropapillary pattern reported here had significantly worse clinical outcomes than patients whose tumor lacked this invasion pattern²².

Correlations between genotype and phenotype

There is also increasing interest in understanding relationships between genotype and morphologic phenotype. Our group previously reported that many *BRCA*-associated HGSCs demonstrate “SET pattern” morphology along with numerous tumor-infiltrating lymphocytes; relationships between SET pattern morphology and pushing pattern metastasis were also described.^{1,3} The Brigham group recently validated these associations and expanded on them by linking the presence of SET-pattern architecture in the primary site with relatively favorable clinical outcomes.²³ This group also, intriguingly, hypothesizes a dualistic model of high grade serous carcinogenesis in *BRCA1* mutation carriers, one arm of which is characterized by young age, low prevalence of serous tubal intraepithelial carcinoma (STIC), SET morphology, and favorable clinical outcomes. Indeed, we found 2 mutually exclusive patterns of peritoneal metastasis in *BRCA1* germline mutation carriers, one with favorable outcomes (SET and either exclusively or predominantly pushing pattern metastases) and one with destructive invasion by micropapillae.

The Cancer Genome Analysis (TCGA) subclassified HGSCs into 4 genomically defined, mostly exclusive groups: immunoreactive, proliferative, differentiated, and mesenchymal.⁹ The immunoreactive group harbored the most cases with germline *BRCA* mutation, best sensitivity to platinum-based chemotherapy, and most favorable clinical outcomes, while the mesenchymal group contained fewer cases with *BRCA* germline mutations; carcinomas in this category also featured platinum insensitivity and very poor clinical outcomes. As tumor cells were not microdissected, categorization as immunoreactive or mesenchymal must have derived, at least in part, from the tumor microenvironment. If this assertion is true, then the immunoreactive tumors would have large numbers of tumor infiltrating immune cells, while the mesenchymal tumors would exhibit intermingling of tumor cells with host stroma. Although it was not clearly defined whether the case material was limited to tissue from the adnexa or metastatic sites, we speculate that “immunoreactive” tumors are closely aligned with SET-pattern and pushing pattern metastasis, particularly those with many tumor infiltrating lymphocytes, and “mesenchymal” tumors are more likely to show destructive patterns of invasion that feature intermingling of epithelial cells and stroma, including infiltrative micropapillae. Along these lines, radiologists from our institution have recently published the results of genomic-radiologic correlations that assert strong relationships between “immunoreactive” HGSCs and round peritoneal tumor nodules on one hand, and between “mesenchymal” HGSCs and destructively infiltrative metastases that frequently involve the intestinal mesentery.²⁴ Finally, the TCGA study concluded that incorporating HGSC group assignment along with *BRCA* status provided optimal outcome predictions⁹.

The data presented here are similar to those of a different cohort reported previously by our group.^{1,3} The cohort of 102 HGSCs represented patients with: 1) sporadic HGSCs lacking *BRCA* abnormalities; 2) sporadic HGSCs with *BRCA1* promoter methylation, somatic *BRCA1* mutation, or somatic *BRCA2* mutation; or 3) patients carrying a germline mutation in either *BRCA1* or *BRCA2*. We reported that exclusively or predominantly pushing pattern metastases were confined to patients with *BRCA1* or *2* aberration, whether or not the aberration was a germline mutation. Pushing pattern metastases were found in 76% of patients or tumors with *BRCA* aberration, a figure similar to that reported here, while the remaining patients had micropapillary-only infiltrative metastases. With only rare exceptions, patients with pushing pattern metastases had primary site tumor showing SET architecture. Patients whose tumors had intact *BRCA* all had mixed pattern infiltrative metastases without any pushing pattern metastases or purely micropapillary infiltration. Although we did not assess the reproducibility of our criteria for classifying patterns of peritoneal metastasis in the current study, the previous study reported that only 2 cases were classified differently by 2 observers working independently, which suggests that our criteria are reproducible.

Conclusion

In conclusion, most *BRCA1* mutated HGSCs and almost all *BRCA2* germline mutated HGSCs studied lack destructive invasion patterns in metastatic sites. Patients with metastases featuring pushing invasion patterns have more favorable clinical outcomes than do patients with destructive patterns. Differences in the distribution of pushing pattern

metastases among *BRCA1* and *BRCA2* germline mutation carriers possibly account for more favorable clinical outcomes in the *BRCA2* group.

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Figure 1.
Pushing pattern metastases: (A) Low-power; (B) High-power.

Figure 2.
Irregularly infiltrating patterns of metastasis: (A and B) Micropapillary infiltrative; (C)
Infiltration by combinations of solid nests and micropapillae (mixed pattern).

Figure 3.
Architecture: (A) Predominantly papillary; (B) Solid; (C) Pseudo-endometrioid or cribriform; (D) Transitional cell-like.

Figure 4.

Distribution of invasion patterns and tumor architecture.

*reflects median distribution of each pattern. For example, “67%” means that pushing pattern predominant cases contained pushing pattern metastases that constituted 2/3 of metastases, on average, in each case.

Table 1

The distribution of tumor architecture and pattern of invasion in metastatic sites, stratified by the type of *BRCA* germline mutation.

Genetic subgroup	Tumor architecture (predominant pattern)	Patterns of invasion	No. of cases
<i>BRCA1</i> germline (n=23)	Solid	PP	12
	Papillary	PP	4
	Pseudoendometrioid	PP	1
	Micropapillary	MIP	6
<i>BRCA2</i> germline (n=14)	Solid	PP	10
	Papillary	PP	3
	Micropapillary	MIP	1

Abbreviations: PP, pushing pattern; MIP, micropapillary infiltrative pattern; IP, infiltrative pattern.