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ORIGINAL ARTICLE

Histopathologic Features of High Grade Serous Ovarian Carcinomas Associated with BRCA Mutation

Shradha Sivadas[1], Tejas Vidwans[2], Vidya Chandraprabha[3], Indu R. Nair[4], Wesley M. Jose[5]

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ABSTRACT

Background: High-grade serous ovarian carcinoma (HGSOC) is frequently associated with homologous recombination repair (HRR) deficiency due to BRCA1/2 mutations. Recognition of characteristic histopathological patterns in BRCA-mutated and HRD-positive tumours has diagnostic and therapeutic relevance.

Objective: To identify distinctive histomorphological features associated with BRCA mutated and/or HRD-positive HGSOC and correlate them with clinicopathological parameters.

Methods: A retrospective observational study was conducted. Of the 333 histologically confirmed HGSOC cases (2018–2024), 48 underwent BRCA testing, and 9 had concurrent HRD analysis. Archival haematoxylin and eosin (H&E) slides were reviewed for SET morphology (solid, pseudo-endometrioid, transitional), necrosis, nuclear pleomorphism, mitotic index, and tumour infiltrating lymphocytes (TILs). Clinical and molecular data were retrieved, and statistical associations were analysed using Chi-square and Fisher's exact tests.

Results: Among 48 tested cases, BRCA1 mutations were identified in 25% and BRCA2 in 2.1%; 33.3% (16/48) were BRCA / HRD positive. BRCA/HRD-positive tumours showed significantly higher frequencies of necrosis, high mitotic activity, lymphovascular invasion, and SET pattern. The odds of BRCA/HRD positivity were approximately 13–17 times higher in tumours exhibiting SET morphology. TILs were more frequent but not statistically significant.

AUTHOR'S AFFILIATION:

[1] Oncopathology Fellow, Amrita Institute of Medical Sciences, Kochi, Kerala, India.
[2] Oncopathology Fellow, Amrita Institute of Medical Sciences, Kochi, Kerala, India.
[3] Assistant Professor, Amrita Institute of Medical Sciences, Kochi, Kerala, India.
[4] Professor, Amrita Institute of Medical Sciences, Kochi, Kerala, India.
[5] Clinical Professor, Department of Medical Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.

CORRESPONDING AUTHOR:

Indu R. Nair, Professor, Department of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.

E-mail: indurn@aims.amrita.edu

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Conclusion: One-third of HGSOC cases demonstrated BRCA and/or HRD positivity, correlating strongly with distinctive histopathological features, suggestive of underlying genomic instability. Recognition of these morphological surrogates can guide targeted molecular testing and optimize therapeutic stratification for PARP inhibitor therapy. Identification of these specific histological features may guide in molecular testing especially in resource limited settings.

KEYWORDS

• High-Grade Serous Ovarian Carcinoma • BRCA1 • BRCA2 • Homologous Recombination Deficiency • Set Pattern • Parp Inhibitor • Histopathology • India

INTRODUCTION

High-grade serous ovarian carcinoma (HGSOC) represents the most common and lethal subtype of epithelial ovarian cancer, accounting for nearly 70% of ovarian cancer related deaths globally.[1] It is characterized by rapid progression, genomic instability, and poor prognosis despite advances in cytoreductive surgery and chemotherapy. A pivotal discovery in recent decades has been the strong association between HGSOC and germline or somatic mutations in the BRCA1 and BRCA2 genes, which are integral to the homologous recombination repair (HRR) pathway responsible for repairing double-strand DNA breaks. Loss of BRCA function results in homologous recombination deficiency (HRD), genomic instability, and heightened chemosensitivity features that underpin the therapeutic rationale for PARP inhibitor (PARPi) therapy.[2,3]

The lifetime risk of ovarian cancer is approximately 40–60% in BRCA1 and 10–30% in BRCA2 mutation carriers.[4]

In India, ovarian cancer remains the third most common gynaecologic malignancy, with 45,701 new cases and 32,077 deaths reported in 2020.[5] High-grade serous carcinoma constitutes about 50–65% of all epithelial ovarian cancers in Indian cohorts,[6] and germline BRCA1/2 mutations are detected in 10–20% of affected women.[7] The median age of onset tends to be slightly earlier than in Western populations,[6] and most patients present at advanced stages (FIGO III–IV) due to vague symptoms and absence of screening programs, resulting in poor five-year survival rates of 30–40%.[8]

Histologically, BRCA-mutated and HRD-positive HGSOCs often exhibit distinctive morphological variants collectively termed the SET pattern comprising solid, endometrioid-like, and transitional like growth patterns.[9] These tumours frequently display high mitotic activity, necrosis, and prominent tumour infiltrating lymphocytes (TILs), reflecting underlying genomic instability. Although aggressive in morphology, such tumours often show enhanced chemosensitivity and improved outcomes, particularly in BRCA2-mutated cases.[10] Recognition of these features can aid in identifying patients who warrant BRCA/HRD testing and may benefit from PARP inhibitor based targeted therapy.[11]

Given the clinical and therapeutic implications, correlating histomorphological features with BRCA and HRD status is essential to refine diagnostic accuracy, guide molecular testing, and optimize personalized management in HGSOC.

We did this study to identify the distinctive histomorphological findings of BRCA-associated high-grade ovarian carcinomas and their association with various clinicopathological factors.

MATERIALS AND METHODS

This is a retrospective observational analysis conducted at a single tertiary care centre. The study was carried out in the Department of Pathology in collaboration with the Department of Medical Oncology, after institutional ethical committee clearance.

Haematoxylin and Eosin (H&E) stained slides of histopathologically confirmed consecutive cases of serous ovarian carcinoma diagnosed between January 2018 and December 2024 were retrieved. Cases with inadequate tissue for evaluation and those who received post-neoadjuvant chemotherapy (NACT) were excluded. H&E slides were independently reviewed by two pathologists to assess the following histomorphological features.[12]

SET Pattern: Defined as >25% of the tumour showing solid (figure 1), pseudo-endometrioid (figure 2), or transitional cell differentiation (figure 3).

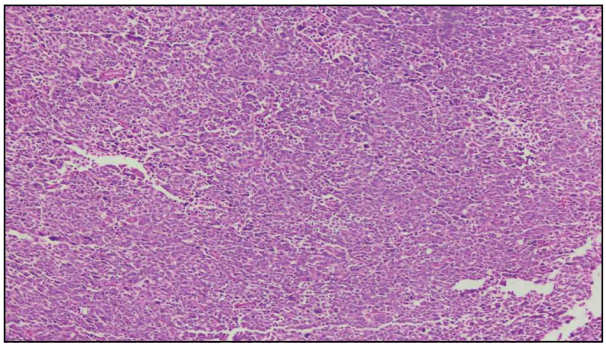

Figure 1: Solid growth pattern (BRCA+)

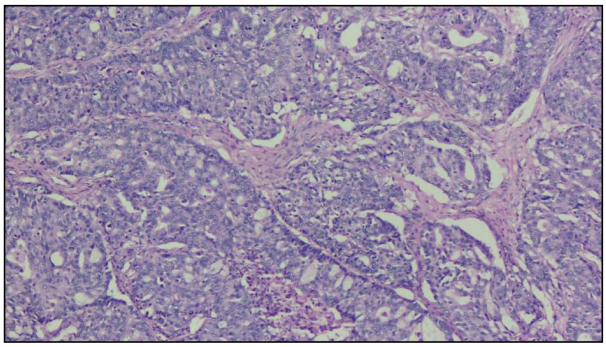

Figure 2: Pseudo-endometrioid pattern (BRCA+)

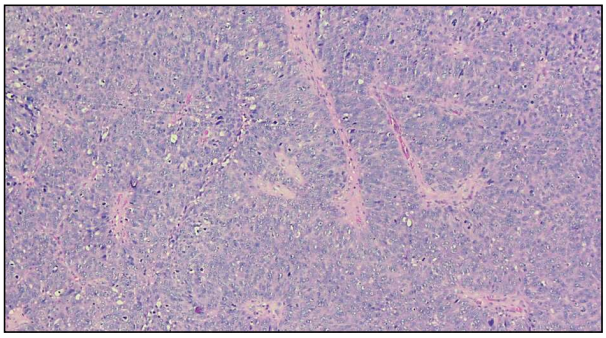

Figure 3: Transisitional pattern

- Necrosis: Evaluated as either comedo-like or geographic necrosis.
- Nuclear Pleomorphism: Scored based on irregular nuclear features using a modified Nottingham grading system.

Mitotic Activity: Categorized as:

- Low [≤12 mitoses per 10 high-power fields (HPFs)]
- Intermediate (13–24 mitoses/10 HPFs)
- High (≥25 mitoses/10 HPFs)
- TILs: Considered positive when >40 intraepithelial lymphocytes were present per HPF.

Relevant clinical data, including demographic profile, BRCA mutation status, capsular rupture, and lymph node metastasis, were obtained from the hospital information system.

Details of BRCA mutation testing were retrieved, which included both germline and somatic mutations. The following molecular techniques were used for BRCA assessment.[13]

Next-Generation Sequencing (NGS)

Multiplex Ligation-dependent Probe Amplification (MLPA)

Homologous Recombination Deficiency (HRD) testing

Statistical analysis was performed using SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA). The following statistical methods were applied:

Fisher's Exact Test and Chi-square Test were used for the analysis of categorical variables.

Odds ratio (OR) was calculated to assess the strength of association between variables.

A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 333 cases of confirmed high-grade serous carcinoma were identified. Among these, 48 cases underwent BRCA testing. Of these, 12 cases (25%) were BRCA-positive, comprising 11 BRCA1-positive and 1 BRCA2-positive cases 36 cases (75%) were BRCA-negative.

Overall, 15 cases were positive for either HRD or BRCA, while 33 cases were negative for both HRD and BRCA.

Mean age of the patients was 57.31 years (± 10.4 years).

In the subset of 13 cases with BRCA positivity, SET pattern was seen in 10 as against 8 out of 35 BRCA negative cases. Lymph node metastasis and lymphovascular invasion was seen in 6 cases, necrosis in 12, prominent nuclear pleomorphism in 11 cases and high mitotic in 12 cases. Extraovarian spread was seen in 11 cases and significant TILs, in 6.

On combining both BRCA HRD cases (total-15), SET pattern was in 12 cases. 8 showed lymph node metastasis, 10 showed

lymphovascular invasion, and 5 showed significant TILs. All cases showed necrosis, prominent nuclear pleomorphism and extra ovarian spread. 14 showed high mitotic activity.

DISCUSSION

High-grade serous carcinoma (HGSC) remains the most prevalent and lethal subtype of epithelial ovarian cancer, characterized by genomic instability and widespread TP53 mutations. A significant proportion of HGSCs harbour defects in the homologous recombination repair (HRR) pathway, most notably due to germline or somatic mutations in BRCA1 or BRCA2 genes, and more broadly, homologous recombination deficiency (HRD).[14] Understanding the prevalence and pathological correlates of BRCA/HRD status is therefore critical for stratifying patients for targeted therapies, particularly PARP inhibitors (PARPi).

In the present study, 333 histologically confirmed cases of HGSC were identified, of which 48 underwent BRCA testing, and 9 also underwent HRD analysis. Among those tested, BRCA1/2 mutations were found in 25% (12/48), and BRCA1 in 22.9% (11/48) BRCA2 mutation in 2.1% (1/48), with 72.9% (35/48) showing no BRCA mutation. Notably, when HRD testing was added, an additional 3 cases were HRD-positive and BRCA-negative, underscoring that HRD testing captures a subset of genomically unstable tumours not identified through BRCA analysis alone. In total, 31.2% (15/48) were either BRCA or HRD positive, while 68.7% (33/48) were negative for both. This prevalence is consistent with prior studies showing that up to 50% of HGSCs may exhibit HRD, though BRCA mutations alone account for 15–30%.[14]

Histopathological analysis revealed significant associations between BRCA/HRD status and key morphological features. Necrosis was significantly more frequent in BRCA/HRD-positive tumours ($p = 0.001$), a finding previously reported in studies indicating higher tumour proliferation and apoptotic rates in BRCA-deficient tumours.[15] High mitotic activity, another hallmark of BRCA-associated tumours, also showed a strong association in our cohort ($p = 0.001$), reinforcing the notion that BRCA/HRD-positive tumours are biologically more aggressive yet more responsive to DNA-damaging agents.[16]

One of the most striking findings was the prevalence of the SET pattern (solid, pseudo-endometrioid, and transitional like morphology) in BRCA and/or HRD-positive tumours. A significant difference ($p < 0.00001$) was observed compared to BRCA/HRD-negative cases.

We found that the odds of having a BRCA mutation are 17 times higher in tumors with a SET pattern than those without. The odds of being HRD/BRCA mutated are 13×higher in SET pattern tumors (figure 4). This pattern, once considered a morphological variant, has emerged as a surrogate histological indicator of HRD. McAlpine et al. first described the association of SET morphology with BRCA mutations and platinum sensitivity, suggesting it reflects underlying genomic instability.[17] Soslow *et al*. further elaborated that tumours with SET features often show extensive necrosis, lack of papillary architecture, and high TILs, correlating with HRD phenotype and better clinical outcomes with PARPi.[18]

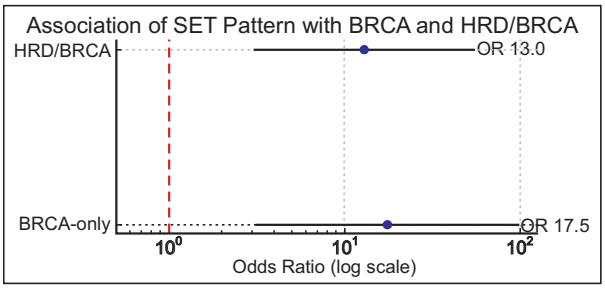

Figure 4: The odds of having a BRCA mutation are ~17 times higher in tumors with a SET pattern than those without. The odds of being HRD/BRCA mutated are ~13× higher in SET pattern tumors.

Lymphovascular invasion (LVI) and lymph node metastases were also more frequent in BRCA/HRD-positive tumours, with significant p-value (0.018) These findings may suggest a paradox wherein BRCA/HRD-positive tumours exhibit locally aggressive behaviour but retain enhanced chemosensitivity due to defective DNA repair.[19] Additionally, while prominent nuclear pleomorphism and extraovarian spread were observed in both BRCA-positive and BRCA/HRD-positive groups, no significant differences were detected, possibly indicating that these are more universal features of HGSC irrespective of HRR status.

Tumour infiltrating lymphocytes (TILs), though previously described as more frequent

in BRCA1-mutated tumours due to increased neoantigen load,[20] did not show a statistically significant association in our cohort (p = 0.2). This discrepancy may reflect sample size limitations or intratumoral heterogeneity. Nevertheless, the observed trend warrants further exploration, especially in the context of immunotherapy responsiveness.

The higher proportion of SET morphology in HRD/BRCA (66.7%) compared with BRCA-only tumours (55.6%) further supports the notion that HRD extends beyond germline BRCA1/2 mutations to include other genomic events leading to homologous recombination failure. Thus, SET morphology may serve as a unifying histopathologic indicator of global HRD status rather than BRCA mutations alone. This underscores the need to incorporate HRD testing alongside BRCA analysis for more accurate molecular stratification. Data from major clinical trials such as ARIEL 3 and PRIMA have shown that BRCA-wildtype, HRD-positive patients derive significant benefit from PARP inhibition, further supporting expanded HRD profiling.[21]

These findings have profound therapeutic implications. Patients with HRD-positive tumours, even in the absence of BRCA mutations, may qualify for maintenance PARP inhibitor therapy. The 2020 FDA approval of niraparib for maintenance therapy in platinum-sensitive, HRD-positive HGSC patients, regardless of BRCA status, further validates this approach. From a pathology perspective, recognizing surrogate histological markers like SET pattern, necrosis, and mitotic activity can guide clinicians toward prioritizing molecular testing in selected cases, especially in resource-constrained environments.

In conclusion, this study demonstrates that a significant subset of high-grade serous carcinoma (HGSC) cases harbour BRCA mutations (25%) and/or homologous recombination deficiency (HRD), with a combined prevalence of 31.3%. These alterations show strong associations with distinct histopathological features, particularly necrosis, high mitotic activity, and the SET pattern, all of which may serve as morphological surrogates for underlying genomic instability. From an oncopathologist's perspective, recognizing these morphological cues and integrating them with molecular findings can aid in identifying patients likely to benefit from PARP inhibitor therapy.

LIMITATION

Limitations of this study include the small number of HRD-tested cases, which restricts deeper statistical comparisons. Larger cohorts with uniform HRD scoring and integration with clinical outcomes are needed to validate these findings.

Author Contributions

Conceptualization: Indu R Nair, Shradha, Tejas,. Data curation: Shradha, Wesley, Formal analysis Shradha, Tejas, Investigation: Wesley, Indu, Vidya, Methodology: Shradha, Indu, Wesley. Project administration: Indu. Resources: Shradha, Tejas, Vidya. Supervision: Indu. Validation: Indu, Wesley, Writing – Shradha, Indu. Writing - review & editing- Shradha, Indu, Tejas, Vidya.

Ethics statement

All procedures performed in the current study were approved by IRB and/or national research ethics committee (reference number ECASM-AIMS-2025-312, dated 31/07/25) in accordance with the 1964 Helsinki declaration and its later amendments." Formal written informed consent was not required with a waiver by the appropriate IRB.

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Data availability statement: Data supporting these findings are available within the article or upon request.

Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Amrita institute of medical sciences.

Informed consent statement: it is taken during surgery.

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